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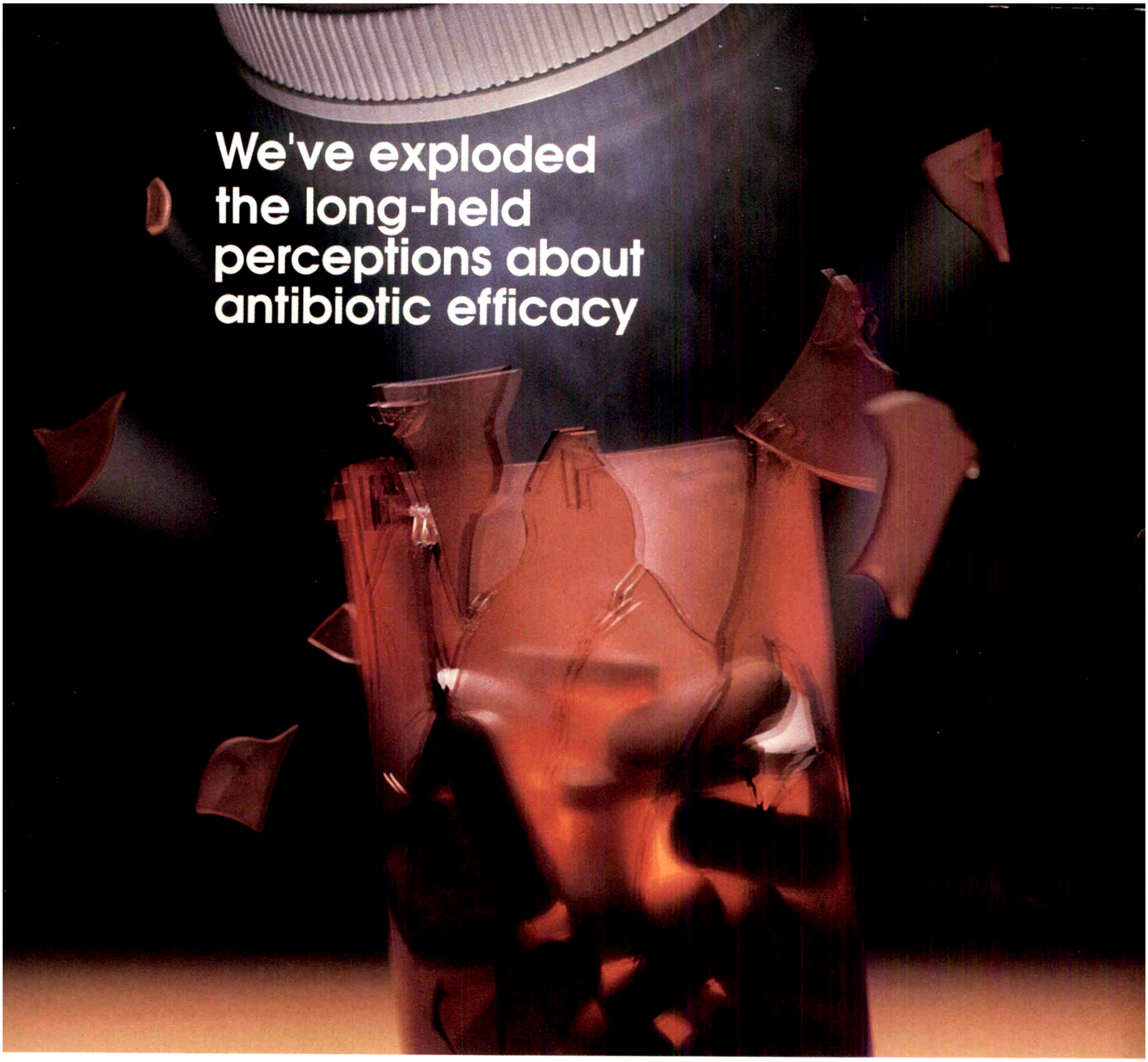
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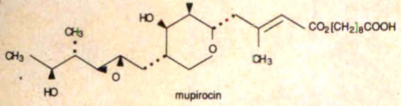

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THE PEDIATRIC FORUM

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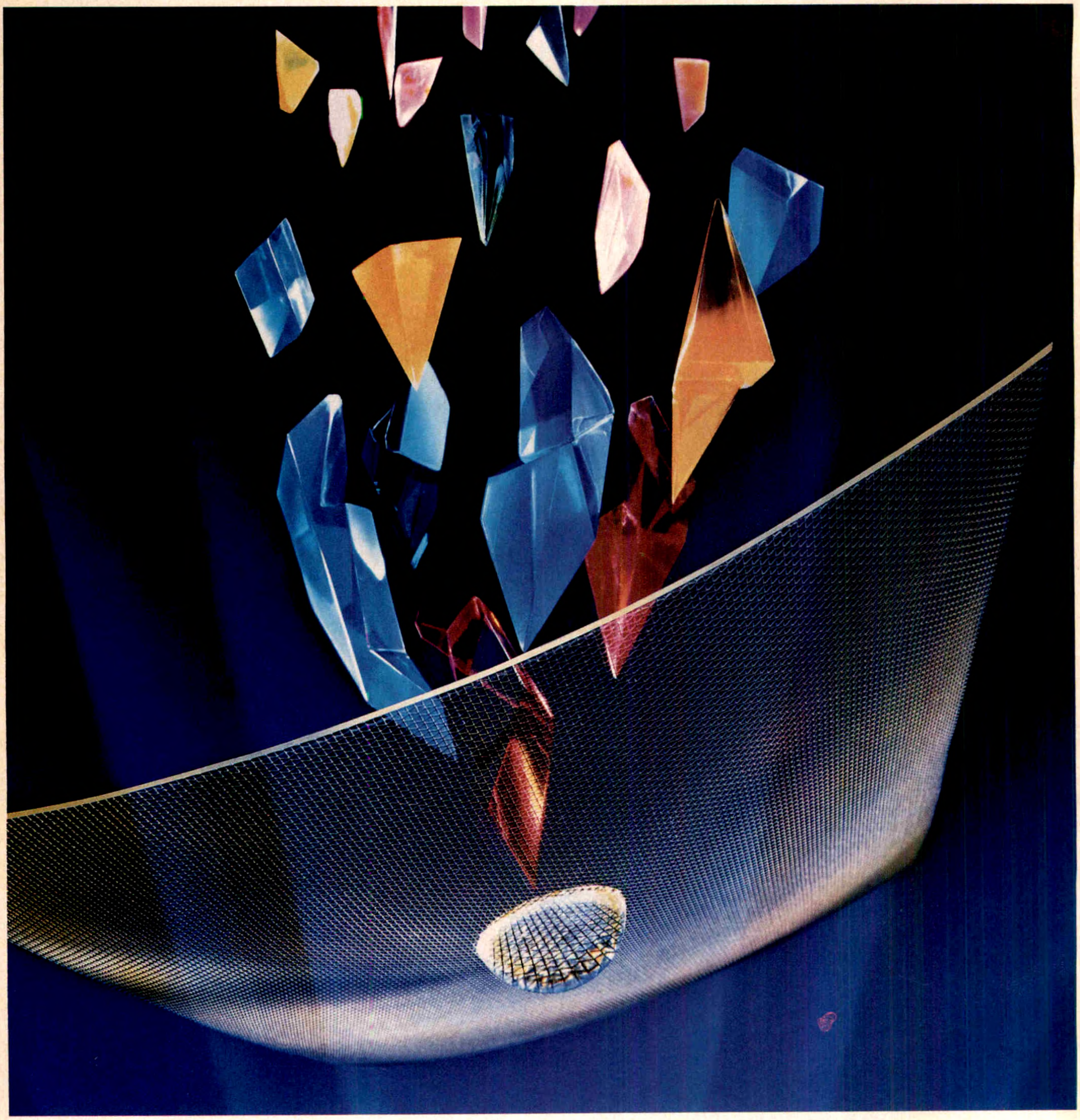

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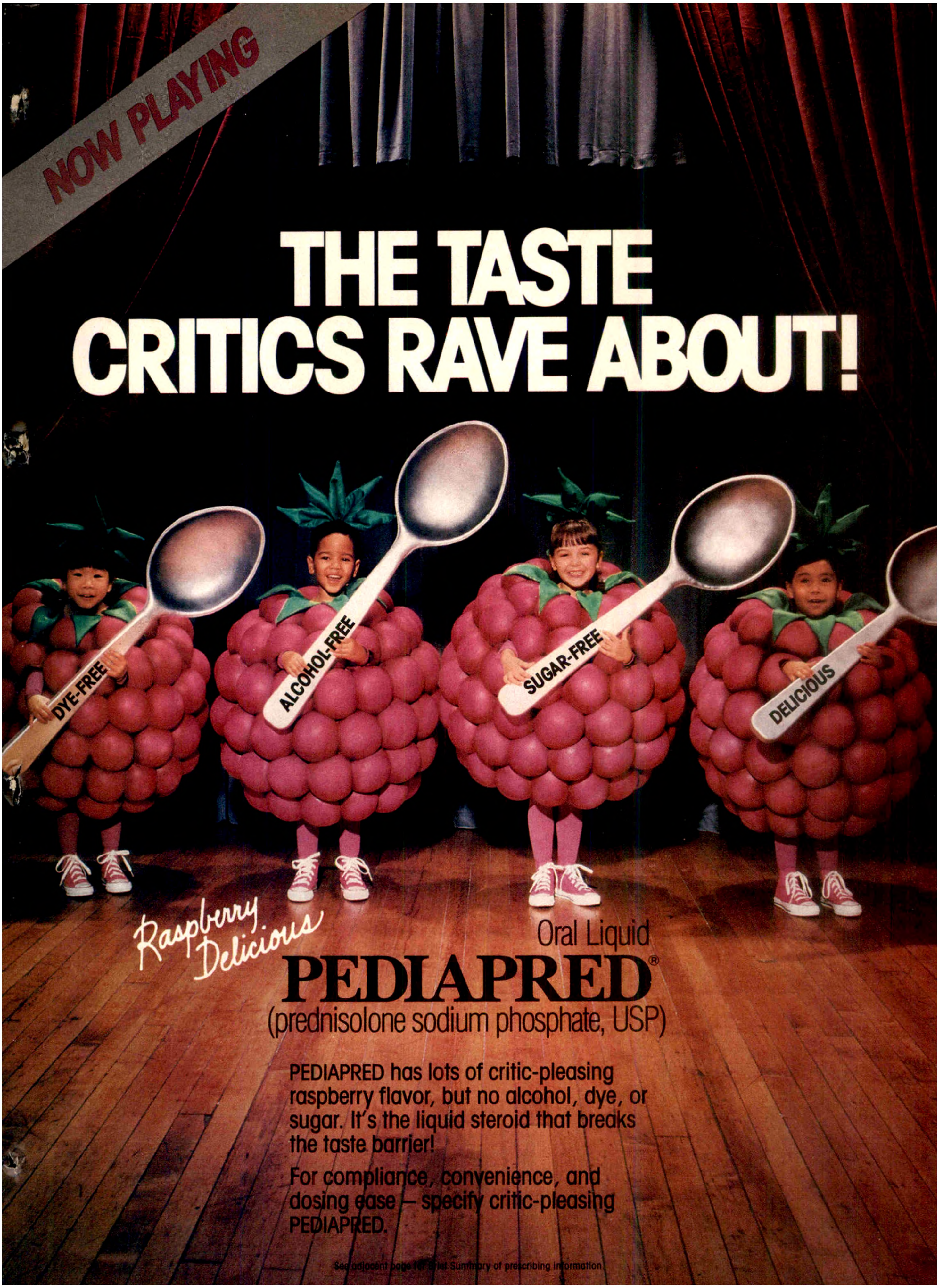

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Hemorrhagic Shock and Encephalopathy

Clinical Definition of a Catastrophic Syndrome in Infants

Enrique Chaves-Carballo, MD; Jorge E. Montes, MD; W. Britt Nelson, MD; Blair A. Chrenka, MD

• We treated nine infants who unexpectedly developed shock, seizures, and fever, followed by diarrhea, consumption coagulopathy, and hepatorenal dysfunction. Despite vigorous treatment, three infants died and all except one of the six survivors have severe residual neurologic abnormalities. Postmortem findings included cerebral edema, white matter petechial hemorrhages, gastrointestinal hemorrhages, and fatty liver. These clinicopathologic features are similar to those previously described in 10 infants as being due to hemorrhagic shock and encephalopathy, except for the presence of fatty liver in our patients. Based on the combined experience of 19 infants, we propose diagnostic criteria for hemorrhagic shock and encephalopathy that may facilitate recognition and differentiation from other shock syndromes in infancy.

(*AJDC.* 1990;144:1079-1082)

In 1983, Levin et al[1] described the clinicopathologic features of hemorrhagic shock and encephalopathy (HSE) among 10 infants who had rapid onset of shock, seizures, and fever, followed by disseminated intravascular coagulation (DIC), diarrhea, acidosis, and hepatorenal dysfunction. Despite aggressive medical support, seven infants died and three survived with severe neurologic deficits. Cerebral edema, gastrointestinal hemorrhages, and hepatocellular degeneration were described. No consistent bacterial, viral, or toxic causative agent was demonstrated. Fifteen additional patients with HSE were recently described by Levin et al.[2]

See also p 1077.

Nine infants admitted to Children's Hospital of The King's Daughters, Norfolk, Va, between 1980 and 1986 had similar clinical courses to cases of HSE reported from Great Britain.[1-5] We believe that HSE represents a distinct clinical entity and propose diagnostic criteria to facilitate its recognition and differentiation from sepsis, toxic shock syndrome, hemolytic-uremic syndrome, and infantile Reye's syndrome.

PATIENTS AND METHODS

Clinical Features

The clinical features in our patients are summarized in Table 1. All infants were between 1 and 6 months of age, five were male, and four were black. All except one infant (patient 7) had been previously healthy. A prodrome had been present for 1 to 7 days in four infants. All had abrupt onset of a catastrophic illness manifested by respiratory arrest (four infants), coma (two infants), or seizures (three infants). Initial examination usually indicated that the infants were in shock (blood pressure, <50 mm Hg), febrile (rectal temperature, 38.9°C to 42.2°C), and in a coma (Glasgow Coma Scale[6] scores, <8). The clinical courses were marked by refractory shock; persistent seizures; metabolic acidosis; electrolyte imbalance; and profuse, foul-smelling, guaiac-positive diarrhea in all but two infants. Several hours after admission, clinical evidence of consumption coagulopathy appeared in the form of excessive bleeding from venipuncture sites or gastrointestinal hemorrhage, with moderate to severe hepatomegaly developing subsequently. Despite intensive efforts to combat shock, fever, DIC, seizures, and neurologic deterioration, three infants died and five survived with severe neurologic deficits. The remaining patient, a 5-month-old infant (patient 6), received dantrolene sodium (1 mg/kg) intravenously before transport to our hospital. On arrival, his temperature was 41.3°C, and he survived with only moderate sequelae.

Laboratory Studies

Routine laboratory studies on admission showed leukocytosis and thrombocytopenia (Table 2). Prolonged prothrombin and partial thromboplastin times, decreased fibrinogen levels, and positive fibrin split products suggested the presence of DIC. Increased aminotransferase values (range, 324 to 2000 U/L) were found in all those tested, while blood ammonia concentrations were normal in all except one patient (patient 9). Increased serum bilirubin values were found in all infants (range, 1.6 to 6.7 mg/dL), increased lactic dehydrogenase levels in three infants (range, 1650 to 3888 U/L), and increased creatinine phosphokinase levels in one infant (1456 U/L). Initial serum concentrations of albumin, potassium, and calcium were normal. Hypoglycemia was not found in any infant. Abnormal renal function, on the other hand, was commonly encountered with azotemia, hypernatremia, and metabolic acidosis. Other laboratory studies, including serum and urine toxicologic and metabolic screens, cerebrospinal fluid analysis, and bacterial and viral cultures of blood, urine, stool, and cerebrospinal fluid, failed to show any consistent abnormality. The results of neurophysiologic studies, including electroencephalograms, brain-stem auditory-evoked responses (BAERs), and somatosensory-evoked responses (SSERs), are shown in Table 3. Electroencephalographic studies showed diffuse slowing or

---

Accepted for publication January 8, 1990.

From the Departments of Neurology (Dr Chaves-Carballo), Pediatrics (Drs Chaves-Carballo, Montes, Nelson, and Chrenka), and Pathology (Dr Chrenka), Eastern Virginia Medical School and Children's Hospital of The King's Daughters, Norfolk. Dr Chaves-Carballo is now with Kansas University Medical Center, Kansas City.

Presented as preliminary reports at the Child Neurology Society meetings, Memphis, Tenn, October 12, 1985, and San Antonio, Tex, October 14, 1989, and at the San Diego Pediatric Critical Care Symposium, San Diego, Calif, March 5, 1987.

Reprint requests to the Department of Pediatrics, Kansas University Medical Center, 39th and Rainbow Boulevard, Kansas City, KS 66103 (Dr Chaves-Carballo).

epileptiform activity in seven infants. The BAER studies showed normal patterns in four of five patients studied, while SSER studies revealed attenuated or absent cortical responses in all five infants.

Treatment

On admission to the intensive care unit, respiratory distress and hypotension were treated vigorously with endotracheal intubation, mechanical ventilation, and aggressive fluid resuscitation. Shock was particularly difficult to combat and often required large volumes of fluids. Vasoactive agents were used to support blood pressure in three infants and anticonvulsant drugs were necessary to control seizures in five infants. After initial management, treatment of prerenal failure and electrolyte abnormalities was by conservative management in all except one infant (patient 5) who developed acute tubular necrosis and required peritoneal dialysis. Cerebral resuscitation measures, such as hyperventilation, osmodiuretics, and pentobarbital sodium, were also implemented when necessary to attempt control of cerebral edema. Consumption coagulopathy was managed aggressively with packed-cell transfusions, fresh-frozen plasma, platelet infusions, and vitamin K. Despite such intensive therapy, four of the infants died and five of six survivors had severe neurologic deficits.

Pathologic Studies

Postmortem studies in three infants showed cerebral edema, scattered petechial hemorrhages of the white matter, pneumonitis, gastrointestinal hemorrhages, and hepatic centrilobular necrosis. Clear evidence of DIC with fibrin deposition was found in only one infant (patient 3). Light microscopic examination of skeletal muscle showed no abnormalities. Of particular interest was the presence of fatty metamorphosis of the liver in all three patients whose specimens were examined histologically. These fatty changes differed from those found in Reye's syndrome in that both microdroplet and macrodroplet deposition was evident in hepatocytes. Other less common abnormalities were tubular degeneration (patient 5) and subendocardial vacuolation (patients 3 and 5).

Table 1.—Clinical Features in Nine Infants With Hemorrhagic Shock and Encephalopathy

Patient/Age, mo/Sex	Prodrome*	Onset	Blood Pressure, mm Hg	Temperature, °C
1/1/M	Fever (1 d)	Respiratory arrest	<50	39.8
2/1/M	None	Respiratory arrest	<50	40.4
3/3/M	None	Seizures	46	41.1
4/2/F	None	Seizures	40	41.6
5/5/M	Fever (2 d)	Respiratory arrest	46	42.3
6/5/M	URI (1 d)	Unresponsive	36	41.3
7/6/M	None	Seizures	48	. . .
8/2/F	URI (7 d)	Unresponsive	72	41.1
9/1/F	None	Respiratory arrest	60	37.6

*URI indicates upper respiratory tract infection.

Table 2.—Laboratory Values in Nine Infants With Hemorrhagic Shock and Encephalopathy*

Patient	WBC Count, $\times 10^9$/L	Platelet Count, $\times 10^9$/L	PT, s	PTT, s	Ammonia Level, μmol/L	AST, U/L
1	68.0	46.0	15	57	. . .	. . .
2	10.3	42.0	>100	>200	10	592
3	12.2	59.0	44	51	29	596
4	14.4	20.0	25	82	29	1240
5	14.3	79.0	>100	>200	43	2000
6	21.9	76.0	28	69	42	324
7	20.9	64.0	18	32	40	428
8	12.4	69.0	19	34	. . .	555
9	10.4	30.0	>100	>200	91	1539

*WBC indicates white blood cell; PT, prothrombin time; PTT, partial thromboplastin time; and AST, aminotransferase.

Table 3.—Neurophysiologic Findings in Nine Infants With Hemorrhagic Shock and Encephalopathy

Patient	Electroencephalogram	Brainstem Auditory-Evoked Responses	Somatosensory-Evoked Responses
1	. . .	. . .	. . .
2	Diffuse slow	. . .	. . .
3	Delta 2 generalized	. . .	Absent
4	Suppression 1	Normal	. . .
5	Delta 2 generalized	. . .	Attenuated
6	Delta 2 generalized	Normal	Absent
7	Diffuse slow	Prolonged	Absent
8	Normal	Normal	. . .
9	Spikes bilaterally	Normal	Absent

COMMENT

The 1983 report by Levin et al[1] from The Hospital for Sick Children (London, England) of 10 patients with HSE was followed by the recognition of similar patients[3-5] in Great Britain. Patients with HSE were also reported from North America,[7,8] the Netherlands,[9] and Israel.[10] A joint surveillance study by the British Hospital Paediatric Society and Communicable Disease Surveillance Centre collected 44 cases of HSE between 1982 and 1984.[5] Diagnostic criteria lacked uniformity, however, and some patients included in the British surveillance report[5] did not conform to the typical features delineated by Levin et al[1]: six had hyperammonemia, five had normal renal function, and four had no evidence of DIC. The patients from North America similarly differed from typical instances of this disorder because of the absence of DIC[7] and occur-

Table 4.—Diagnostic Features in 19 Patients With Hemorrhagic Shock and Encephalopathy*

Diagnostic Feature	Levin et al,[1] 1983	Present Series
Prodromal illness (n = 11)		
URI	1	2
Vomiting	4	0
Fever	1	2
Diarrhea	1	1
Listlessness	1	0
Encephalopathy (n = 19)		
Unresponsive	10	2
Seizures	10	3
Respiratory arrest	...	4
Shock (n = 17)	10	7
Fever (n = 18)		
>38°C-39°C	7	1
>39°C-40°C	1	1
>40°C	2	6
DIC (n = 19)		
GI bleeding	10	9
Skin bleeding	6	9
Thrombocytopenia	10	9
Prolonged PT	10	8
Prolonged PTT	10	8
Fibrin split products	10	8
Hepatic dysfunction (n = 18)		
AST level, >500 IU/L	10	8
ALT level, >500 IU/L	10	8
Normal ammonia level	10	7
Renal dysfunction (n = 18)		
Elevated BUN level	10	8
Elevated creatinine level	10	8
Hypernatremia	10	8
Metabolic acidosis	10	8

*Values represent numbers of patients. URI indicates upper respiratory tract infection; DIC, disseminated intravascular coagulation; GI, gastrointestinal; PT, prothrombin time; PTT, partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; and BUN, blood urea nitrogen.

Table 5.—Proposed Diagnostic Criteria for Hemorrhagic Shock and Encephalopathy in Infants

1. Age at onset during infancy (usually 2-10 mo)
2. Acute encephalopathy (respiratory arrest, seizures, or coma)
3. Fever (rectal temperature, 39°C)
4. Shock (blood pressure, <50 mm Hg)
5. Disseminated intravascular coagulation (excessive bleeding from skin, mucous membranes, or gastrointestinal tract; coagulopathy demonstrated by thrombocytopenia [$<100 \times 10^9$/L], prolonged prothrombin time, prolonged partial thromboplastin time, decreased fibrinogen level, and fibrin split products)
6. Hepatic dysfunction (abnormal aminotransferase values greater than threefold upper limits of normal)
7. Normal blood ammonia values
8. Renal dysfunction (azotemia, hypernatremia, or metabolic acidosis)
9. Exclusion of similar infantile conditions (eg, septic shock, toxic shock syndrome, Reye's syndrome, and hemolytic-uremic syndrome)

rence beyond infancy.[8] Levin et al[2] have recently described additional patients up to the age of 14 years.

We propose diagnostic criteria for HSE in infants that may facilitate its early recognition and exclusion of other infantile shock syndromes. These diagnostic criteria are based on the salient clinical features as described by Levin et al[1] and found by us in a combined total of 19 children (Table 4). All infants were between 1 and 8 months of age. About half of the patients developed a prodromal illness characterized by upper respiratory tract symptoms, vomiting, diarrhea, fever, or listlessness. Onset of the encephalopathy was abrupt and heralded by respiratory arrest, seizures, and shock. Rectal temperature was usually greater than 39°C, and blood pressure was less than 50 mm Hg. Disseminated intravascular coagulation and hepatorenal failure developed within 48 hours after admission. Blood glucose and blood ammonia levels were, with rare exceptions, normal. A list of diagnostic features of HSE is presented in Table 5.

The nosologic status of HSE remains controversial.[11,12] Bacon et al[13-17] and Aujurd et al[18,19] have described similar disease as being due to heatstroke. In the past, heatstroke in infants was commonly ascribed by pediatricians to overwrapping. Hemorrhagic shock and encephalopathy occur more often between 2 and 10 months of age, which represents a vulnerable period for thermoregulatory balance. Heat production per unit of surface area reaches a maximum after 5 months, while heat loss by sweating develops more slowly during the first year of life.[20,21] Lack of sweating despite hyperpyrexia has been noted in infants with heat stroke and blamed on autonomic nervous system failure.[21] Thermoregulatory imbalance has also been implicated in sudden infant death syndrome,[22-24] and a muscle membrane abnormality has been identified among families of children who have died of sudden infant death syndrome. Hyperpyrexia in young kittens results in high mortality with or without accompanying seizures.[25] Thus, hyperpyrexia seems to be a common denominator in several catastrophic illnesses of infancy, such as heat stroke, sudden infant death syndrome, and HSE.

Pathologic reports have provided insufficient information about the central nervous system in infants who died of heatstroke. The limited descriptions by Bacon et al[13] and Aujurd et al[18] suggest that cerebral edema and petechial hemorrhages may be typical findings in both heatstroke and HSE. Adults who die of heatstroke show evidence of severe endothelial injury at the precapillary level, which results in DIC, cerebral edema, and petechial hemorrhages.[26]

Although a comparable ultrastructural lesion has not been demonstrated in HSE, it is possible that heatstroke and HSE in infants may be closely related, if not identical, disorders.

Levin et al[1] emphasized that HSE and Reye's syndrome may be differentiated on the basis of hyperammonemia and fatty liver. All except one of our patients also lacked hyperammonemia, but detailed histologic examination of the liver with fat stains from three autopsied patients with HSE revealed *both* microdroplet and macrodroplet fatty infiltration in addition to centrilobular hepatic degeneration. The specificity of microdroplet fatty infiltration of the liver in Reye's syndrome has recently been questioned. Bonnell and Beckwith[27] found similar fatty changes in the liver from 21 children who had died of traumatic or sudden unexpected causes. Whether fatty liver is an important component of HSE requires clarification by more detailed histopathologic or ultrastructural study. Reye's syndrome in infants presents more often with seizures and hypoglycemia.[28] Furthermore, shock, hyperpyrexia, and DIC are unusual features of Reye's syndrome at any age.

Hemolytic-uremic syndrome may present in infancy with clinical features that resemble HSE. Age predilection, microangiopathic hemolytic anemia, hepatic involvement, hypertension, neurologic complications, and renal pathologic features, however, allow differentiation of hemolytic-uremic syndrome from HSE.[29] Similarly, the possibility that HSE may be a form of toxic shock syndrome has been considered.[30] Although many clinical similarities exist between toxic shock syndrome and HSE, the rapid onset of multisystem involvement and profound shock contrasts with the paucity of pathologic findings in toxic shock syndrome.[31] Furthermore, extensive toxicologic and bacteriologic investigations have failed to demonstrate evidence of a consistent pathogen or toxin in HSE. A possible role for the increased trypsin and decreased α_1-antitrypsin plasma concentrations reported by Levin et al[1] requires further investigation.

In our patients, electroencephalographic studies yielded nonspecific findings and showed diffuse slowing compatible with toxic-metabolic encephalopathy or postictal state (Table 3). Serial electroencephalograms, in contrast, proved to be helpful in monitoring the clinical course, particularly when neurologic assessment was limited by mechanical ventilation and neuromuscular blockade. Evoked potentials were of prognostic value, as reported for other comatose children.[32] In addition, SSER studies showed attenuated or absent cortical responses in four children and correlated with severe neurologic disability or death.

The case-fatality ratio in our series compares favorably with that in the infantile cases described by Levin et al[1] (44% vs 66%). Early diagnosis and rapid institution of therapy may have contributed to improved survival. One of our patients (patient 9) received dantrolene per our advice before transfer to our intensive care unit; his outcome was more favorable compared with the other survivors: a follow-up examination 1 year later showed only moderately severe neurologic deficits. Whether early administration of dantrolene to patients with HSE is beneficial remains to be seen. Hemodialysis and plasmapheresis have been used unsuccessfully in one patient.[33] Despite such vigorous therapeutic measures, the prognosis in HSE remains poor. Application of diagnostic criteria such as we propose for HSE may result in earlier recognition and intervention.

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New Muscle Power Test in Neuromuscular Disease

Feasibility and Reliability

Emanuel Tirosh, MD; Oded Bar-Or, MD; Peter Rosenbaum, MD, FRCP

• We studied the feasibility, reliability, and reproducibility of an "all-out" 30-second cycling or arm cranking test of muscle power and muscle endurance (the Wingate Anaerobic Test) in 66 girls and boys aged 5 to 18 years old who had cerebral palsy or a myopathy. The arm and leg tests, given in duplicate, were feasible in 94% and 61% of subjects, respectively. Reliability coefficients exceeded .95 in patients with spastic cerebral palsy and myopathies and were somewhat lower in those with athetotic cerebral palsy. Means and SDs were similar in both trials. We conclude that the Wingate Anaerobic Test is feasible, highly reliable, and reproducible in these patients.

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Physically disabled children often have poor physical fitness, which may compromise their daily physical function. Affected fitness components include muscle strength (the maximal force that can be generated at a given joint angle), muscle power (the mechanical work performed per unit of time), muscle endurance (the ability to sustain force or power), range of motion, and maximal aerobic power (often referred to as "aerobic fitness"). The degree to which these components are affected in any given patient depends on specific pathophysiologic processes and on the stage of the disability.[1] To formulate an effective therapeutic/rehabilitative approach, the onus is on the clinician to identify the affected fitness component, assess the degree of deficiency, and prescribe accordingly.

Although some fitness components of the disabled—notably maximal aerobic power[2-4]—have been measured in the laboratory, others (mostly muscle strength and range of motion) have traditionally been assessed clinically as part of a physical examination. Clinical assessment of muscle function has included, among others, grading of strength by manual testing[5-8] and the rating of functional abilities.[9,10] Such methods, although widely used, depend on the dexterity, experience, and interpretation of the clinician, which potentially compromises their objectivity and reliability.[8] They also depend on the cooperation and motivation of the child.

In contrast, laboratory-based measurements of muscle function are usually more standardized, objective, and reliable. So far, such measurements have been limited to the strength of the disabled child, where force is measured by a myometer,[7,11] cable tensiometer,[12] strain gauge dynamometer,[13] or isokinetic dynamometer.[4,14] The only published test of muscle endurance in pediatric neuromuscular disease is based on measurement of the time that a supine child can hold his or her neck or straight leg 45° from the ground.[15,16] This test, although simple, was found difficult to standardize and of low reliability.[16]

In 1974, a test was developed at the Wingate Institute, Natanya, Israel, for measuring muscle power and muscle endurance in able-bodied children and adults.[17] This 30-second all-out cycling or arm cranking Wingate Anaerobic Test (WAnT) was subsequently shown to be extremely reliable.[18-20] It was validated against other indexes of short-term, high-intensity exercise,[17] the preponderance of fast-twitch muscle fibers,[21] and glycolytic activity in the muscle.[22,23] The WAnT seems responsive to changes in performance induced by training.[24] More details were given by Bar-Or.[25]

The purpose of this study was to evaluate the suitability of the WAnT for children and adolescents with neuromuscular disease. Specifically, we wanted to assess its feasibility, reliability, and reproducibility as a test of upper- and lower-limb power and endurance.

SUBJECTS AND METHODS

Subjects

Sixty-six girls and boys aged 5 to 18 years old from southwestern Ontario, Canada, were recruited. The study was approved by the ethics committee of McMaster University, Hamilton, Ontario. Informed consent was signed by the subject or, in case of minority, by a parent. Thirty-eight subjects had cerebral palsy (CP), 27 with spasticity, 10 with athetosis, and one with athetosis and ataxia; and 28 had other conditions, including Duchenne's (n = 13) or Becker's (n = 5) muscular dystrophy, spinal muscular atrophy (n = 5), congenital muscular atrophy (n = 2), central core myopathy (n = 1), myotonic dystrophy (n = 1), and Charcot-Marie-Tooth disease (n = 1). Physical characteristics, by diagnostic groups, are summarized in Table 1.

Diagnosis was based on clinical presentation, muscle enzymes levels, muscle biopsy results, or electromyography, as relevant. Classification of CP was made according to published taxonomy.[26] No subjects with congestive heart failure, respiratory failure, exercise-induced bronchoconstriction, fever, or acute infection were included in the cohort.

Design and Procedures

Each subject made two visits to the laboratory. Visit 1 included a questionnaire about the subject's habitual activity[27]; medical assessment and the PULTIBEC (*p*hysical activity, *u*pper limb, *l*ocomotion, *t*oilet, *i*ntelli-

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From the Hannah Khoushy Child Development Center, Haifa (Israel) Medical Center (Rothschild), Faculty of Medicine, Technion–Israel Institute of Technology (Dr Tirosh); and the Department of Pediatrics (Drs Bar-Or and Rosenbaum), Children's Exercise and Nutrition Centre (Dr Bar-Or), and Chedoke Child and Family Centre (Dr Rosenbaum), McMaster University, Hamilton, Ontario, Canada.

Reprint requests to Children's Exercise and Nutrition Centre, Chedoke Hospital Division, Box 2000, Station A, Hamilton, Ontario L8N 3Z5, Canada (Dr Bar-Or).

Table 1.—Physical Characteristics of Subjects by Gender and Diagnostic Groups

	Mean ± SD											
	Spastic Cerebral Palsy			Athetotic Cerebral Palsy			Duchenne's Muscular Dystrophy			Other Neuromuscular Disorders		
Variable	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
N	15	12	**27**	6	5	**11**	13	0	**13**	9	6	**15**
Age, y	11.0 ± 3.0	12.0 ± 3.3	11.4 ± 3.1	12.0 ± 2.9	11.4 ± 3.5	11.7 ± 3.1	13.2 ± 2.9	...	13.2 ± 2.9	12.8 ± 4.5	12.1 ± 2.7	12.5 ± 3.7
Height (arm span), cm	141.2 ± 10.9	140.2 ± 12.8	140.8 ± 17.8	140.6 ± 14.7	138.5 ± 11.4	39.6 ± 13.2	150.6 ± 11.8	...	150.6 ± 11.8	152.3 ± 22.2	140.6 ± 15.7	147.6 ± 20.7
Weight, kg	34.8 ± 13.0	38.2 ± 14.7	36.3 ± 13.9	31.5 ± 8.8	34.4 ± 10.6	33.0 ± 9.8	46.7 ± 13.2	...	46.7 ± 13.2	44.9 ± 20.0	32.5 ± 10.9	39.9 ± 18.0
Total of 4 skin folds, mm	26.6 ± 5.0	43.6 ± 18.0	33.8 ± 14.9	19.8 ± 4.4	33.4 ± 9.3	26.6 ± 10.0	71.2 ± 24.8	...	71.2 ± 24.8	45.7 ± 23.0	46.2 ± 24.4	45.9 ± 23.5

Table 2.—Feasibility of the Wingate Anaerobic Test by Diagnostic Group (Sexes Combined)*

	No. (%) Completing Test			
Group	**Arms**	**Legs**	**Arms and Legs**	**Neither**
Spastic CP	27 (100)	24 (89)	24 (89)	0 (0)
Athetotic CP	10 (91)	5 (45.5)	5 (45.5)	1 (9)
Duchenne's MD	10 (76.9)	2 (15.4)	2 (15.4)	3 (23.1)
Other neuromuscular diseases	15 (100)	9 (60)	9 (60)	0 (0)
Total	**62** (93.9)	**40** (60.6)	**40** (60.6)	**4** (6.1)

*CP indicates cerebral palsy; MD, muscular dystrophy.

gence, behavior, eyes, communication) assessment of functional capacity,[28] performed by a pediatrician; body weight (subject sitting on a calibrated clinic scale, accurate to 100 g); height (stadiometer) or length by body segments (Harpenden anthropometer) in subjects who could not stand erect; arm span (anthropometer); and skin-fold thickness in triplicate (Harpenden caliper) from the right triceps, biceps, subscapular, and suprailiac sites. The child then performed the WAnT twice, once by cycling and once by arm cranking, with a 45- to 60-minute rest in between. The sequence for these two tests was randomized.

For a detailed description of the WAnT, see Bar-Or[25] and Dotan and Bar-Or.[20] Briefly, this is a 30-second cycling or arm cranking test at "all-out" speed, against a constant braking force (Fleisch-Metabo mechanical ergometer, with pedal revolutions read continuously by a counter, connected on-line to a computer; other ergometers and simpler means of counting pedal revolutions can be used as well). This force is predetermined to yield initially a mechanical power that is two to three times the subject's maximal aerobic power. This power, however, cannot be sustained for more than a few seconds, and it subsequently declines.

The pedal length and seat and handlebar positions were adjusted to suit each subject's size and were duplicated in visit 2. The cycling pedals were equipped with toe clips. The arm cranking pedals were cylindrical. When necessary, the subject's shoe or hand was taped to the pedal. The arm cranking test was done with the subject sitting on her or his own wheelchair, with the height of the pedal axle adjusted to shoulder height.

The test was preceded by a 4-minute warmup (pedaling or arm cranking at a mild pace, which yielded a heart rate of 110 to 130 beats per minute), interspersed by four all-out sprinting trials of 2 to 3 seconds each. These trials were used for learning the sprinting task, as well as for determining the braking force that would subsequently be used in the test. A 3-minute rest period separated the warmup from the test. On the command "start," the subject started pedaling at maximal speed. Encouragement was given throughout the 30-second period. The test was followed by 2 to 3 minutes of leisurely pedaling or arm cranking against zero force. Two performance indexes were calculated: peak power (the highest mechanical power at any 3-second period) and mean power (the power averaged over 30 seconds). These were calculated both in watts and in watts per kilogram of body weight.

At visit 2, the cycling and arm cranking tests were repeated with the use of protocols identical to those at visit 1, but in a reverse sequence.

Data Analysis

On the basis of the activity questionnaires, the subject was defined as sedentary (no physical activities at all), slightly active (less than 1 hour of total exercise per week at school or outside school), moderately active (2 hours per week), highly active (up to 6 hours per week at school or with a team), or athletic (6 or more hours per week of training or competing). Body adiposity was calculated as the sum of the four skin folds.

Pearson's Product-Moment Correlation was used to establish test-retest reliability in the WAnT. A paired t test was used to determine reproducibility.

A WAnT was considered feasible if the subject could complete it. To define the factors that best characterized those subjects who were able to perform the test and those who could not, a stepwise discriminant analysis was performed. The statistic examined in this analysis was Wilks' λ. The following variables were included in the stepwise analysis: age, Tanner stage, diagnosis, activity level, adiposity, physical performance according to the PULTIBEC scale, and limb function according to this scale.

RESULTS

Feasibility

The ability to complete the WAnT was not gender related. The following results therefore refer to both sexes combined. Of the 66 subjects, 62 (94%) successfully performed the arm cranking test at least once. Fifty-eight (88%) completed it twice. The leg cycling test was completed once by 40 (61%) and twice by 38 (58%). Every subject who completed the cycling test could also complete the arm cranking test. Table 2 is a breakdown of completion according to diagnostic groups. The WAnT was particularly feasible for the patients with spastic CP and least feasible for those with Duchenne's muscular dystrophy. It is noteworthy (last column in Table 2) that, excluding the Duchenne's muscular dystrophy group, only one patient (with athetotic CP) could perform neither the cycling nor the arm cranking task.

Reproducibility and Reliability

Table 3 displays the mean power and peak power scores by diagnostic groups and gender. The means and variances in each subgroup (and in the sample as a whole) were similar when the two duplicate tests were compared. None of the between-test differences was significant. Overall, test-retest reliability coefficients for the whole sample ranged from .935 to .976 (Table 4). Apart from the group with athetotic CP, *r* values exceeded .95 in each of the subgroups. Figures 1 and 2 represent the individual data for peak power (lower limbs) and mean power (upper limbs), respectively, again displaying a strong agreement between the duplicate tests. A similar pattern was obtained for the peak power of the upper limbs and the mean power of the lower limbs.

Table 3.—Reproducibility of Limb Performance (Peak and Mean Power) in the Duplicate Tests by Diagnostic Group and Gender*

		Mean ± SEM			
		Peak Power, W		Mean Power, W	
Group	Sex	Test 1	Test 2	Test 1	Test 2
		Upper Limbs			
Spastic CP	M	79.9±15.8	78.8±17.1	56.1±12.0	55.7±13.4
	F	76.4±18.2	67.5±15.3	54.9±12.9	45.2±10.0
Athetotic CP	M	17.3±6.9	19.7±8.3	11.9±4.7	11.8±4.9
	F	23.5±2.9	23.5±2.9	18.6±2.1	16.8±2.8
Duchenne's MD	M	23.1±7.8	20.6±6.7	15.8±5.7	12.0±4.1
Other NMD	M	95.6±33.8	94.2±33.7	69.1±24.3	63.2±21.6
	F	12.7±4.8	12.0±3.5	6.9±2.9	6.3±2.2
		Lower Limbs			
Spastic CP	M	179.4±37.4	195.6±39.7	146.1±31.0	151.9±31.8
	F	160.9±34.9	167.2±29.9	119.5±21.9	130.7±22.0
Athetotic CP	M	86.0±22.5	82.3±33.8	66.9±21.9	56.1±26.6
	F†	...	...	...	...
Duchenne's MD	M†	...	...	...	...
Other NMD	M	210.9±54.7	201.2±52.0	151.5±44.5	162.9±43.6
	F‡	...	...	...	...

*CP indicates cerebral palsy; MD, muscular dystrophy; and NMD, neuromuscular disorders. All differences between duplicate scores are nonsignificant.

†Only two children had duplicate values.

‡Only one child had duplicate values.

Table 4.—Test-Retest Correlation of Peak Power and Mean Power by Diagnostic Groups (Genders Combined)*

	Upper Limb		Lower Limb	
Group	Peak Power	Mean Power	Peak Power	Mean Power
Spastic CP				
n	25	25	23	23
r	.950	.956	.962	.952
Athetotic CP				
n	9	9	5	5
r	.967	.915	.697	.822
Duchenne's MD				
n	9	9	2	2
r	.996	.990	...	...
Other NMD				
n	15	15	8	8
r	.996	.992	.984	.976
Total				
n	**58**	**58**	**38**	**38**
r	.935	.976	.962	.962

*CP indicates cerebral palsy; MD, muscular dystrophy; and NMD, neuromuscular disorders.

COMMENT

The main finding in this study was the high test-retest reliability and reproducibility of the WAnT when performed by children and adolescents with a neuromuscular disease. Similarly, high test-retest reliabilities of the WAnT have been described for healthy children ($r = .95$ to .97)[29] and healthy adults ($r = .91$ to .97).[30-32] A test-retest reliability of .89 was obtained in 18 elderly people with chronic obstructive lung disease who performed an abbreviated version of the WAnT (O.B.-O., L. Berman, MD, unpublished data, 1988). Good reliability and reproducibility of the WAnT have also been found under various climatic conditions,[20] several states of hydration,[19] and various motivational settings.[33]

The high reliability and reproducibility in our young patients, irrespective of their neuromuscular disability, represents a major advantage of the WAnT over the previously published clinical test of muscle endurance.[15,16] In the latter, the supine child holds his or her neck or a straight leg at 45° from the floor for as long as possible. Such a condition is hard to standardize, and, as reported by Hosking and colleagues,[16] this clinical test is poorly reproducible. It is particularly noteworthy that once their hands or shoes were taped to the pedals, even athetotic children achieved similar results in both trials. The above findings have another practical implication: learning seems to play a minor role in performing the WAnT; a patient can reach her or his best result on the first trial, after a brief practice during a 4-minute warmup.

Despite the severity of physical dis-

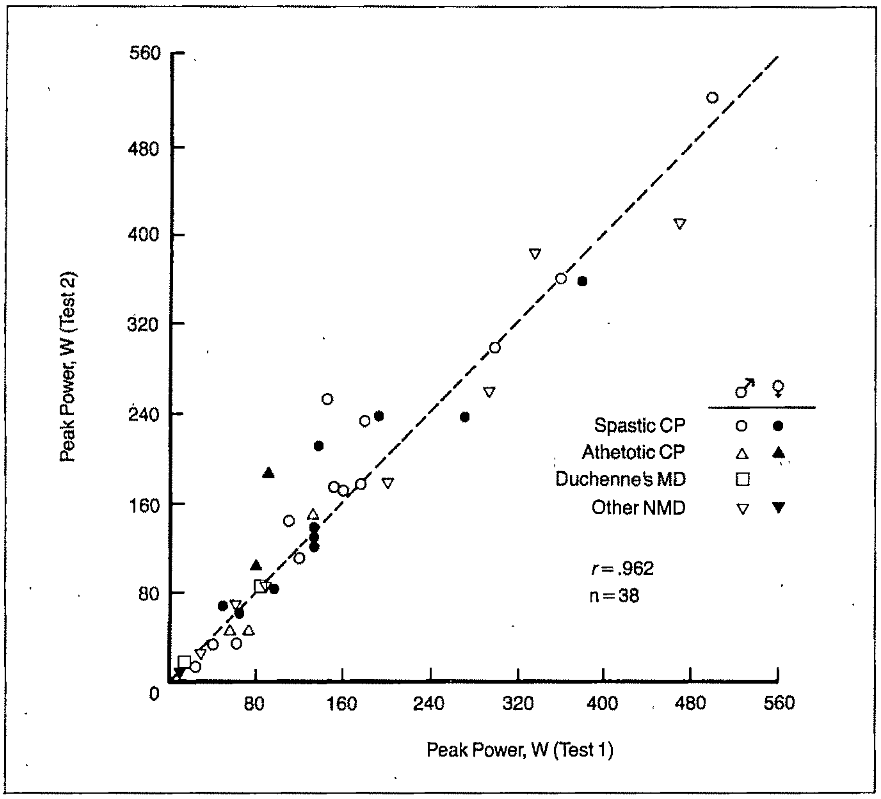

Fig 1.—Test-retest reliability of peak power (lower limbs) during cycling, individual data. Broken line denotes identity. CP indicates cerebral palsy; MD, muscular dystrophy; and NMD, other neuromuscular disorders.

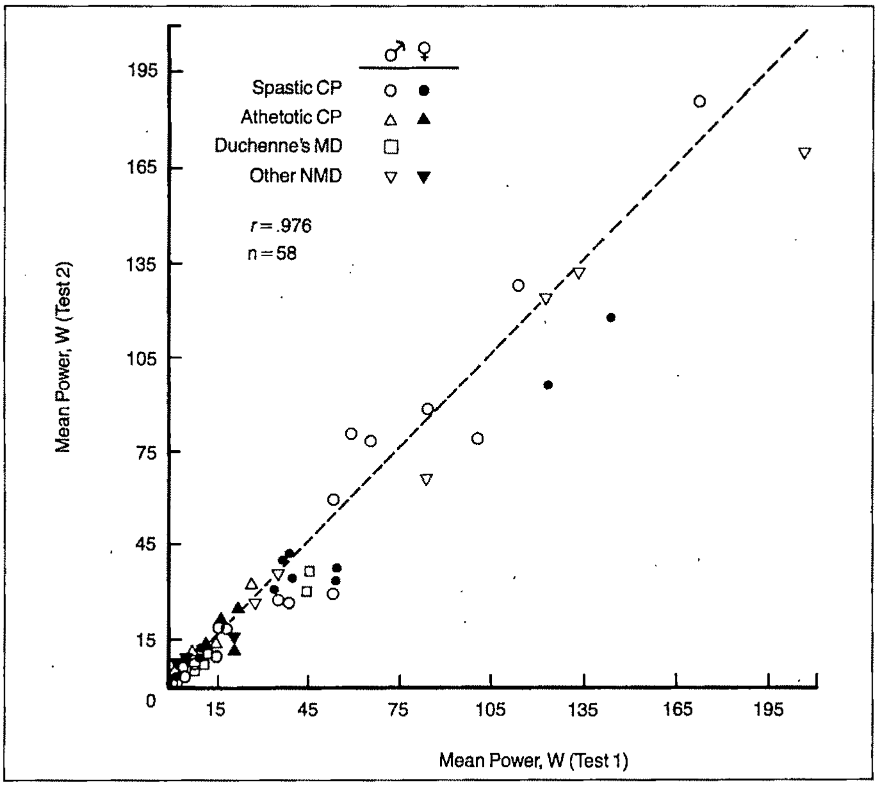

Fig 2.—Test-retest reliability of mean power during arm cranking, individual data. Broken line denotes identity. CP indicates cerebral palsy; MD, muscular dystrophy; and NMD, other neuromuscular disorders.

ability in these subjects, the arm cranking WAnT proved feasible for most (94%) of them, particularly those with spastic CP, non-Duchenne's dystrophy, and muscle atrophy. Even in the group with Duchenne's muscular dystrophy, some 80% managed to complete the arm cranking test. The cycling task was less feasible, but still some 60% of all subjects completed it successfully. This task was particularly hard for the group with Duchenne's muscular dystrophy. This is not surprising, bearing in mind the natural progression of this disease, which, even in early stages, affects large muscle groups in the lower limb, such as the knee extensors. Due to the diversity of disabilities among our patients, it would be hard to establish a general profile of a patient for whom the WAnT is or is not feasible.

Because of the large proportion (93.9%) of subjects who could perform the arm cranking test, the discriminant analysis was used only to predict those who could perform the leg cycling test. It showed that the most important predictor was the functional ability of each of the lower limbs, as assessed by the PULTIBEC scoring system.[28] In 97% of the cases (F[1.60]=163.5, $P<.001$), it predicted correctly a child's ability to perform the cycling test. As a rule, a child who scored 3 or higher in lower-limb function could complete the 30-second test. At this score, the patient can "walk reasonable distances at a moderate pace only" with the help of stick, calipers, or elbow crutches. If the patient can walk short or medium distances only (less than 200 m) at a slow pace or requires armpit crutches or tends to fall when standing (ie, 4 on the PULTIBEC scale), it is not likely that she or he will be able to perform the WAnT cycling test (nor, in all probability, an *aerobic* cycling test). It is noteworthy that once the lower limb function was entered in the discriminant analysis, other predictors such as age, diagnosis, activity level, adiposity, and upper-limb function did not add to the discriminatory power.

This study was not designed to assess the validity of the WAnT as a test of "anaerobic" muscle power and muscle endurance. Previous studies of able-bodied children and young adults have shown performance in the WAnT to be well correlated with other tasks of peak muscle power and local muscle endurance and with biochemical and histochemical indexes of anaerobic muscle metabolism. Of particular interest is the fairly strong positive relationship between peak or mean power and the preponderance of fast-twitch muscle fibers.[21,31] As shown in several studies,[34,35] the fast-twitch fibers in several myopathies are affected more than the slow-twitch fibers are. It is thus possible that the degree of functional deterioration, as assessed by the WAnT, might yield information on the degree of histologic damage in such conditions. This is a subject for further investigation.

The cost of the equipment for this test depends on the type of cycle ergometer and on the manner by which pedal revolutions are counted. The Fleisch ergometer, as used in this project, costs $4000 to $4500. However, much less expensive mechanical ergometers ($800 to $1500) can be used for clinical testing in the physician's office. These ergometers are identical to those widely used for aerobic stress testing of adults. If needed, they can be modified for pediatric populations.[25] They can also be modified for arm testing. Pedal revolutions need to be counted periodically throughout the 30-second test. In this study, a personal computer was connected to the ergometer for automated counting and for on-line calculation of mechanical power. Other, less expensive, methods are also available. The most suitable one for a physician's office would be to mount on the bike a mechanically or electromagnetically tripped electric switch (which will create a pulse each time the pedal passes by it) and connect it to the "standard" lead of an electrocardiograph. By knowing the paper speed of the electrocardiograph, one can then count the pedal revolutions throughout the test.

In conclusion, this study suggests that the WAnT is highly reliable and reproducible for children and adolescents with a neuromuscular disease. Nearly all school-aged patients with disabilities similar to those tested in this study can perform the arm cranking test, and some 60% can perform the cycling test. Based on studies with able-bodied people, the WAnT seems valid for the assessment of anaerobic muscle power and local muscle endurance. Further research is indicated to assess its sensitivity (to training and to functional deterioration) and whether it reflects specific or general changes in fitness.

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Coma Scales in Pediatric Practice

Jerome Y. Yager, MD, FRCPC; Bruce Johnston, PhD; Sahashi S. Seshia, MD, FRCP(C&E)

• Interobserver variability for six coma scales was assessed prospectively on a sample of 15 comatose children, by two physicians, in a double-blind fashion. The six scales were the Glasgow Coma Scale, the Simpson and Reilly Scale, the Children's Coma Score, the Children's Orthopedic Hospital and Medical Center Scale, the Jacobi Scale, and the 0 to IV Scale. Interobserver variability was measured by using disagreement rate and the κ statistic. The results from both methods were generally concordant. The disagreement rate for the various items in the different scales ranged from a high of 0.20 to a low of 0.03. The disagreement rate was greater than 0.10 for verbal responses in the Children's Coma Score and Glasgow Coma Scale and for both items in the Children's Orthopedic Hospital and Medical Center Scale. The disagreement rate was 0.10 or less for the 0 to IV Scale and for all items in the Simpson and Reilly and Jacobi scales. The relatively high interobserver agreement for these scales makes them more suitable for the pediatric setting than the other three scales, since good agreement is essential for interpreting data reliably, both in clinical practice and for research.

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The Glasgow Coma Scale (GCS)[1] is widely used to assess comatose patients. Interobserver agreement for the three items in the original 14-point GCS has been tested in adults who were comatose after head injury[2]. The GCS was described by Teasdale and Jennett[1] from a center dealing mainly with adults, but no information was provided about the ages of patients under study. Many of the responses in the GCS require an adult level of neurodevelopmental function and cannot be easily graded in those under 10 years of age.[3] Therefore, the GCS is not readily applicable to young children suffering from traumatic or nontraumatic coma.[3-6]

Shaywitz[5] suggested that the role of the GCS in assessing children suffering from nontraumatic coma remains to be defined, and Hennes et al[6] recently recommended that "the routine use of the GCS in classifying severity of head injury in children" be reevaluated. A number of other scales have also been described for use in comatose children. Most are based on the GCS. The reliability of a scale is influenced by interobserver agreement. We report the results of a prospective study designed to compare interobserver agreement for six coma scales.

SUBJECTS AND METHODS

Clinical Data

Comatose children admitted to the Pediatric Intensive Care Unit of the Children's Hospital, Winnipeg, Canada, between September 1986 and December 1987, were included in the study provided they could be examined by two observers (J.Y.Y., a junior pediatric neurology fellow, and S.S.S., a senior pediatric neurologist), within a half-hour period of each other (to minimize the possibility of clinical change in the interval) and within 24 hours of admission. Neonates were excluded. The observers did not see each other examine the patients and filled out separate data sheets that listed the items in the six coma scales (Table 1).

The six scales were as follows: the revised 15-point GCS,[7] the Simpson and Reilly (SR) Scale,[3] the Children's Coma Score[4] (CCS), the 0 to IV Scale,[8,9] the Children's Orthopedic Hospital and Medical Center (COHMC) Scale,[10] and the Jacobi Scale.[11]

The investigators did not discuss their interpretation of the terms in the coma scales before the study, and no attempt was made to train the junior observer before or during the study, to minimize training bias and to mimic the clinical practice setting.

The study was approved by the Faculty Committee on the Use of Human Subjects in Research, Faculty of Medicine, University of Manitoba, Winnipeg.

Statistical Data

Data were analyzed at the end of the study period by one of us (B.J.). Three separate methods were used to assess agreement: (1) disagreement rate (DR), as proposed by Teasdale et al[2] (these authors regarded DRs of 0.03 to 0.22 as indicating relatively consistent agreement); (2) the κ statistic[12]; and (3) weighted κ,[13,14] the weights assigned being those described by Fleiss.[14] A κ value of 0 reflects chance agreement; greater than chance agreement leads to positive values of κ, and less than chance agreement leads to negative values.[12] Landis and Koch[15] provided the following "clearly arbitrary," but now generally accepted, guidelines for interpreting κ: less than 0 indicates poor agreement; 0 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 to 1, almost perfect agreement.

RESULTS

Sixteen children met the entry criteria. Data were analyzed for 15 children because one of the two data sheets on patient 7 was misplaced. Their ages ranged from 2 months to 17 years, with a mean age of 3 1/2 years and median of 16 months. Eleven children were comatose from nontraumatic causes and four from traumatic causes. All were intubated at the time of assessment.

The DR for the various items in the coma scales ranged from a high of 0.20 to a low of 0.03 (Table 2). Results obtained with the κ statistic were generally in accordance with those of the DR (Table 2), a lower DR being associated with a relatively higher κ value. The confidence intervals and the P values for κ (Table 2) may be unreliable because of the small sample size and because the κ statistic is only asymptotically normally distributed. There were some differences between the values for individual items obtained with κ and weighted κ statistics. These differences did not alter interpretation. Hence, values for weighted κ are not included in the table.

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From the Section of Pediatric Neurosciences (Dr Yager and Seshia) and Department of Statistics (Dr Johnston), University of Manitoba and Children's Hospital (Drs Yager and Seshia), Winnipeg, Canada.

Read before the XXIII Canadian Congress of Neurological Sciences, Quebec City, Canada, June 16, 1988.

Reprint requests to Section of Pediatric Neurosciences, University of Manitoba, Children's Hospital, 840 Sherbrook St, Winnipeg, Manitoba, Canada R3A 1S1 (Dr Seshia).

Table 1.—Coma Scales in Pediatric Practice*

Scale	Criterion	Score
CCS	Ocular response	
	Pursuit	4
	Extraocular movements intact, pupils reactive	3
	Extraocular movements impaired or pupils fixed	2
	Extraocular movements paralyzed and pupils fixed	1
	Verbal response	
	Cries	3
	Spontaneous respirations	2
	Apneic	1
	Motor response	
	Flexes and extends	4
	Withdraws from painful stimuli	3
	Hypertonic	2
	Flaccid	1
COHMC	Cortical function	
	Purposeful, spontaneous movements	6
	Purposeful voice-evoked movements	5
	Painful stimuli localized	4
	Nonpurposeful movements/global withdrawal	3
	Decorticate posturing	2
	Decerebrate posturing	1
	Flaccidity	0
	Brain-stem function	
	Intact	3
	Depressed	2
	Absent but breathing spontaneously	1
	Absent and apneic	0
0-IV Scale[8,9]	Arouses spontaneously and to stimuli	0
	Stuporous; spontaneous arousal rare; roused readily but briefly by stimuli; cough/gag present	I
	Spontaneous arousal absent; semipurposive/avoidance motor response to stimuli; cough/gag depressed	II
	Arousal in form of motor response only to intense, sustained, painful stimuli; cough/gag absent	III
	Not aroused by even intense, sustained, painful stimuli; cough/gag absent	IV
GCS	Eye opening	
	Spontaneous	4
	To speech	3
	To pain	2
	None	1
	Best verbal response	
	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
	Best motor response	
	Obeys	6
	Localizes	5
	Withdraws	4
	Abnormal flexion	3
	Extensor response	2
	None	1
Jacobi[11]	Best verbal response	
	Fixes, follows, recognizes, laughs	5
	Fixes and follows inconstantly, recognition uncertain	4
	Arouses at times	3
	Motor restlessness, unarousable	2
	Complete unresponsiveness	1
	Best motor response	
	Obeys	5
	Localizes	4
	Flexion	3
	Extension	2
	None	1
	Eyes open	
	Spontaneous	4
	To speech	3
	To pain	2
	None	1
	Oculovestibular response	
	Normal	5
	Tonic-conjugate	4
	Minimal dysconjugate	3
	No eye movements	2
	Nonreactive pupil	1
Simpson and Reilly[3]	Eye opening	
	Spontaneous	4
	To speech	3
	To pain	2
	None	1
	Best verbal response	
	Oriented	5
	Words	4
	Vocal sounds	3
	Cries	2
	None	1
	Best motor response	
	Obeys commands	5
	Localize pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
	Normal aggregate score	
	Birth-6 mo	9
	>6-12 mo	11
	>1-2 y	12
	>2-5 y	13
	>5 y	14

*CCS indicates Children's Coma Score[4]; COHMC, Children's Orthopedic Hospital and Medical Center[10]; and GCS, Glasgow Coma Scale.[7] See original articles for details.

COMMENT

The study was done because information from coma scales is used to make important management decisions, such as determination of prognosis. Assessment of interobserver agreement is desirable under such circumstances and essential if the data are to be used in clinical research[18].

The DR was relatively high (>0.10) for the verbal responses in the GCS and CCS scales, likely reflecting the difficulty in assessing verbal responses in comatose children. Orientation and confusion may be difficult to test even in the conscious child, and verbal responses may be "incomprehensible" by adult criteria.

The DR was also relatively high (0.15) for both items on the COHMC scale. The COHMC and CCS scales give a low score for apnea, and ambiguities may arise in those who are intubated.

The DR was less than 0.10 for the SR Scale. There was less overall disagreement for the items in the SR Scale than for those in the GCS, CCS, and COHMC scales. The DR for the verbal responses in the SR Scale was slightly less than the DR for the verbal response in the Jacobi Scale. Furthermore, the aggregate scores in the SR Scale are age dependent (Table 1). The SR Scale may,

Table 2.—Disagreement Rate (DR) and κ Statistics*

		κ Statistics			
Coma Scales and Items	**DR**	κ	**SE**	**CI**	*P*†
CCS					
Verbal	0.17	0.38	0.14	0.10, 0.66	.003
Ocular	0.08	0.43	0.16	0.10, 0.76	.004
Motor	0.10	0.27	0.16	0.05, 0.59	.047
COHMC					
Cortical	0.15	0.22	0.12	0.01, 0.45	.030
Brain stem	0.15	0.35	0.14	0.07, 0.63	.006
0-IV Scale[8,9]	0.06	0.63	0.16	0.30, 0.93	<.001
GCS					
Verbal	0.20	0.05	0.10	0.13, 0.25	.31
Motor	0.08	0.40	0.12	0.17, 0.63	<.001
Eye opening	0.05	0.30	0.12	0.07, 0.53	.004
Jacobi[11]					
Verbal	0.10	0.22	0.17	0.11, 0.55	.093
Oculovestibular	0.09	0.34	0.12	0.10, 0.58	.003
Motor	0.06	0.49	0.16	0.17, 0.81	.001
Eyes open	0.03	0.45	0.16	0.12, 0.79	.003
Simpson and Reilly[3]					
Verbal	0.08	0.10	0.17	0.24, 0.44	.278
Motor	0.04	0.71	0.15	0.40, 0.02	<.001
Eye opening	0.06	0.29	0.19	0.08, 0.66	.060

*CI indicates confidence interval (95.44%); CCS, Children's Coma Score[4]; COHMC, Children's Orthopedic Hospital and Medical Center[10]; and GCS, Glasgow Coma Scale.[7]

†*P* value is one tailed. The value is for one level of the distribution, the alternate hypothesis being κ = 0.

therefore, be superior to the GCS, CCS, COHMC and Jacobi Scales for the entire age spectrum of pediatric practice.

It has become commonplace to sum the items in the GCS.[16-18] Summed scores are also used to describe coma severity in the CCS, COHMC, Jacobi, and SR scales. Verbal response and eye opening may be difficult to test and score in head-injured patients who are intubated or aphasic or who have swollen eyelids.[19] Levy et al[20] did not find it useful to generate a coma score in their study of nontraumatic coma in adults because many of their patients were intubated.[20] Teasdale et al[16,17] pointed out that the information conveyed by the coma score is less than that contained in the individual three responses and that the three responses are not equally weighted. Hence, information is lost when scores are summed,[16,19] and such scores are inadequate for describing clinical status. Teasdale et al[16] emphasized that each response in the GCS should not only be considered separately but also be supplemented by other neurologic data. Their patients under treatment are never described by the total scores.[17] Starmark et al[18] suggested that "further studies on the reliability of the GCS sum score are needed." These comments on the GCS also apply to scales modeled after it.

The DR was relatively low and the κ value relatively high for the 0 to IV Scale. This scale meets the definition of a "single line scale"[19]; observations are combined for assessing responsiveness, thereby reducing the problem created by intubation, aphasia, and swollen eyelids.[19] All patients in our study were intubated early in their clinical course.

Several methods have been applied to the analysis of interobserver agreement. The simplest and most frequently used is the overall proportion of agreement.[14] This method is satisfactory for binary data but may not reflect the magnitude of disagreement in ordinal or nominal data.[13] We used the DR because it includes and, therefore, conveys information about the degree of disagreement and because it had been previously used to assess observer variability for the GCS.[2]

The κ statistic was also used because it corrects for chance[12] and is now frequently used to assess agreement. Weighted κ was also tried because it has been reported to be superior to κ for ordinal data.[13] Results obtained with κ and weighted κ were not appreciably different in our study.

In our study, results obtained with the use of the DR were generally in accord with those using the κ statistic. A lower DR was usually associated with a relatively higher κ value. The relatively low κ value despite a relatively low DR for the SR verbal response is a reflection of the differences between these two statistical measures of agreement. The low DR suggests that the degree of disagreement was relatively small. The low κ value does not take this factor into account but implies that chance played a major role. We suggest that DR and κ statistics may give complementary information in studies of interobserver agreement, the former providing greater information about the degree of disagreement and the latter mainly assessing the role of chance. Further discussion regarding the relative merits and statistical aspects of DR, κ statistic, and weighted κ in studies of our type is beyond the scope of this article.

Our study was a simultaneous cross-comparison of six coma scales. Absolute values for DR and κ may, therefore, be less important than identifying the scales and items for which interobserver agreement with either or both methods was relatively high. For the same reason, changes in the clinical state in the interval between examinations by the two observers cannot explain differences in interobserver agreement between the scales.

Two possible shortcomings of our study should be addressed. First, only two observers were used. However, ethical and practical considerations limit the number of examiners who can assess a critically ill, comatose child within a short time of each other. In addition, our attempts to involve a pediatric intensivist, a pediatric resident, and Pediatric Intensive Care Unit nurses were unsuccessful because of their multiple clinical commitments. Koran[21] pointed out that studies of clinical reliability "should focus on agreement between two physicians or perhaps three," as this more closely reflects clinical practice. Our results may be influenced by the background of the two observers, one (S.S.S.) a pediatric neurologist and the other (J.Y.Y.) a pediatric neurology fellow. The observers did not discuss the coma scales before or during the study, not only to minimize the bias created by their backgrounds but also to simulate clinical settings; frequently, individuals discussing a comatose child have not had previous deliberations on their respective methods of using a scale.

The second possible shortcoming relates to the sample size of 15. Teasdale et al[2] had 16 patients in their study, and numbers have been similar in several studies of observer variability.[22,23] Sample sizes are limited in studies of our type because of the practical difficulty in getting the same set of observers to examine patients within a short time of each other.[13]

Intraobserver variability cannot be tested in situations such as coma. Clinical findings can change rapidly in such circumstances, and the clinician will be biased by his or her initial examination if the second is repeated too soon after the first.[13]

The age range of patients in our study is representative of that referred to pediatric institutions. The use of a single scale in this population and in such institutions enhances interobserver agreement. Our data suggest that the 0 to IV, SR, and Jacobi scales may be well suited for pediatric practice since interobserver agreement was relatively good for them. Our findings should be considered tentative until confirmed by a study with larger numbers.

Physicians should be aware of the limitations of the GCS and of solely using summed scores generated from such scales to describe comatose children.

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The Effect of Prescribed Daily Dose Frequency on Patient Medication Compliance
Seth A. Eisen, MD, MSc; Douglas K. Miller, MD; Robert S. Woodward, PhD; Edward Spitznagel, PhD; Thomas R. Przybeck, PhD (*Arch Intern Med.* 1990;150:1881-1884)

Linear Growth Response to Exogenous Growth Hormone in Children With Short Stature

I. David Schwartz, MD; Cheng-Shih Hu, MS; Dorothy I. Shulman, MD; Allen W. Root, MD; Barry B. Bercu, MD

• Response to growth hormone (GH) therapy was evaluated in 38 short children (28 males and 10 females; <1% in height for chronologic age [CA]) who were clinically categorized into three groups based on their endogenous mean 24-hour GH concentration (mean 24-hour GH) and peak GH response to two or more provocative agents (peak GH). All patients were treated with biosynthetic somatropin (human growth hormone) (0.15 to 0.30 mg/kg per week) injected subcutaneously three to seven times per week for a mean duration of 12.5 months. Group 1 consisted of 17 subjects (CA, 12.5±2.9 years [mean±SD]; bone age, 9.4± 2.9 years; height velocity [HV], 3.4±1.8 cm/y; peak GH, 5.8±2.6 μg/L; mean 24-hour GH, 1.7±0.6 μg/L; and insulinlike growth factor–I, 0.40±0.24 U/mL. Group 2 consisted of 10 subjects (CA, 11.7±2.7 years; bone age, 9.2±3.0 years; HV, 3.4±1.6 cm/y; peak GH, 16.4±5.2 μg/L; mean 24-hour GH, 1.7±0.5 μg/L; and insulinlike growth factor–I, 0.49±0.27 U/mL. Group 3 consisted of 11 subjects (CA, 12.7±2.2 years; bone age, 10.2±2.4 years; HV, 3.5± 1.5 cm/y; peak GH, 22.5±8.6 μg/L; mean 24-hour GH, 3.8±1.1 μg/L; and insulinlike growth factor–I, 1.07±0.69 U/mL. Following administration of somatropin, an increase (Δ) in HV of 2.0 cm/y or greater occurred in 94% (16/17) of the group 1 subjects (ΔHV of 5.1±2.6 cm/y), in 90% (9/10) of the group 2 subjects (ΔHV of 4.3±2.2 cm/y), and in 73% (8/11) of group 3 subjects (ΔHV of 3.7±2.3 cm/y). However, regardless of provoked and/or endogenous GH secretory dynamics, 88% of the children whose pretreatment HV was 2.0 cm/y or less, 94% whose pretreatment HV was between 2.0 and 4.0 cm/y, and 79% whose pretreatment HV was greater than 4.0 cm/y increased their HVs to 2.0 cm/y or greater while they were receiving somatropin. Significant negative correlations were observed between ΔHV and pretreatment HV ($r = -.67$), ΔHV and GH concentration expressed as a 24-hour area under the curve ($r = -.33$), and ΔHV and peak GH ($r = -.34$). In conclusion, 87% (33/38) of children with stature less than the first percentile, mean HV of 4.0 cm/y or less, and mean bone age of 2.7 years less than CA responded to 1 year of somatropin treatment with acceleration in HV regardless of their endogenous and/or provoked GH values.

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Therapeutic options and strategies have been broadened for treating the short-statured child since the commercial availability of biosynthetic somatropin (human growth hormone). Hence, it has become increasingly important to identify those growth-retarded children who may benefit from somatropin therapy. The question of how to select short children for treatment with somatropin remains unanswered; 24-hour endogenous growth hormone (GH) profiles may detect patients with GH neurosecretory irregularities, but the practical utility of 24-hour GH secretory profiles has been questioned.[1] Prior studies in children with normal provoked GH secretion demonstrated that in 40% to 80%[2-9] of such patients, there was an increase in height velocity (HV) during somatropin therapy. It has been proposed that such patients represent a heterogeneous group and reflect a spectrum of abnormalities in the synthesis and secretion of GH.[9-11] We examined the linear growth response to exogenous somatropin in a heterogeneous group of short, poorly growing children with a variety of GH secretory dynamics.

PATIENTS AND METHODS

The effects of somatropin on linear growth rate were evaluated in 38 short children who had undergone both provocative testing and quantitation of spontaneous secretion of GH. No child had gonadal dysgenesis, malnutrition, or identified underlying systemic or psychologic disease. All patients were euthyroid at the time of study; those patients with central hypothyroidism were receiving thyroxine replacement. The heights of all but one patient were less than the first percentile; patient 21 was at the third percentile. All patients underwent testing of GH secretion with two or more pharmacologic agents (0.5 g/kg of arginine intravenously; 0.075 to 0.1 U/kg of insulin intravenously; 250 to 500 mg of levodopa [L-dopa] by mouth; and 0.1 mg/m^2 of clonidine by mouth), as well as 24-hour evaluation (sampling every 20 minutes) of endogenous GH secretion.[8] An adequate GH response was defined as a peak GH concentration (peak GH) to a provocative agent of 10.0 μg/L or greater. (The data were also analyzed, defining normal GH secretion as peak GH response after stimulation of ≥7.0 μg/L. Although the number of patients within each group varied slightly, there were no significant differences in the observations to be presented.) For purposes of statistical analysis, the patients were categorized into three groups (Table).

Group 1

The peak GH response to all provocative testing was less than 10 μg/L (n=17, 14 males and three females); the pretreatment (pre-HV) was 4.0 cm/y or less, with five exceptions as follows: patients 1 and 4 were prepubertal boys growing 5.9 and 6.4 cm/y, respectively; patient 7, a prepubertal girl with deficiencies of thyrotropin and adrenocorticotropin secretion receiving thyroxine and cortisol replacement, was growing 5.0 cm/y; and two pubertal boys (patients 14 and 17) with inappropriately low insulinlike growth factor–I (IGF-I) concentrations for

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From the Section of Pediatric Endocrinology, University of South Florida College of Medicine and All Children's Hospital, St Petersburg, Fla.

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Reprint requests to Department of Pediatric Endocrinology, All Children's Hospital, 801 Sixth St S, PO Box 31020, St Petersburg, FL 33731-8920 (Dr Bercu).

Clinical Summary and Laboratory Data in Patient Groups*

Patient/Sex	CA, y	BMI, kg/m²	Peak GH, μg/L	24-h GH, μg/L	AUC, μg/L·min	IGF-I, U/mL	Pre-HA, y	ΔHA, y	Pre-BA, y	ΔBA, y	Pre-HV, cm/y	ΔHV, cm/y	Pre-HVz BA, y	ΔHVz BA, y	Somatropin Dose, mg/kg per Week	No. of SC Injections/wk
Group 1																
1/M†	7.1	16.6	6.3	2.6	1723	0.30	2.9	1.1	3.3	1.7	5.9	1.0	−1.4	1.8	0.25	3
2/M†	7.8	16.2	7.6	1.0	289	0.33	4.4	1.2	6.0	1.0	3.0	5.3	−3.4	6.3	0.30	3
3/M†	9.8	17.4	6.0	2.0	451	0.26	6.0	0.9	7.0	0.5	1.4	4.7	−5.0	5.2	0.30	3
4/M†	9.8	14.0	3.5	1.5	1112	0.22	7.4	2.0	9.0	2.5	6.4	2.1	1.4	3.3	0.30	3
5/M†	10.0	14.5	6.8	1.3	563	0.54	5.9	1.3	8.0	. . .	3.1	5.0	−3.2	. . .	0.30	7
6/M†	12.0	19.7	8.6	1.6	1140	0.16	7.3	1.3	9.0	1.5	2.9	6.5	−3.2	9.4	0.30	7
7/F†	12.0	17.4	3.5	1.9	663	0.28	6.8	1.5	6.3	1.5	5.0	3.5	−1.1	4.6	0.30	3
8/M	12.1	16.4	3.9	1.2	1223	0.28	6.5	1.5	8.0	1.0	3.2	5.7	−3.1	7.8	0.15	3
9/M†	12.2	15.3	6.3	2.2	1546	0.39	7.1	0.8	10.0	1.3	3.5	2.0	−2.4	3.1	0.30	6
10/F†	12.5	18.5	1.0	<1.0	0	0.22	4.8	1.7	7.8	1.0	0.8	11.3	−5.9	14.3	0.30	3
11/M	14.3	16.0	8.1	2.6	1926	0.94	9.2	1.8	11.5	1.0	0.5	9.1	−6.1	10.3	0.30	3
12/F‡	14.4	17.9	1.0	<1.0	0	0.18	11.8	1.7	12.0	0.0	1.3	6.8	−6.4	6.2	0.30	3
13/M†	14.6	18.6	3.0	1.2	185	0.21	9.7	1.1	11.5	0.0	3.0	4.6	−2.7	6.2	0.30	3
14/M	15.3	26.2	8.4	2.3	915	0.41	11.4	1.8	13.0	1.0	5.7	3.6	−0.8	0.7	0.25	3
15/M	15.3	22.7	7.5	1.0	388	0.55	12.9	1.4	13.3	0.7	3.3	5.6	−3.7	3.2	0.25	3
16/M	15.6	25.5	8.8	2.2	1400	0.81	10.7	1.8	13.0	0.5	3.8	6.3	−2.7	4.6	0.30	3
17/M	17.1	17.3	8.3	2.5	2954	0.79	9.3	2.0	11.5	1.0	5.0	3.4	0.0	2.9	0.30	7
Mean ± SD . . .	12.5 ±2.9	18.2 ±3.5	5.8* ±2.6§‖	1.7 ±0.6‖	969 ±785‖	0.40 ±0.24‖	7.9 ±2.8	1.5 ±0.4	9.4 ±2.9	1.0 ±0.6	3.4 ±1.8	5.1 ±2.6	−2.9 ±2.2	5.6 ±3.5	0.28 ±0.04	3.9 ±1.7
Group 2																
18/M†	7.5	16.1	10.8	2.1	1307	0.32	4.5	1.2	5.5	1.5	4.3	3.3	−2.1	4.2	0.30	3
19/M†	7.8	15.6	13.6	1.2	634	0.23	4.6	1.2	5.0	1.0	2.9	6.5	−3.5	7.1	0.30	3
20/F†	9.2	14.2	21.8	1.9	960	0.67	5.7	1.1	4.5	2.3	7.2	2.5	−1.8	3.2	0.15	3
21/M†	11.0	14.7	11.4	1.8	1462	0.56	8.1	0.9	10.0	0.0	3.8	1.3	−1.9	1.8	0.30	7
22/M‡	12.0	15.4	26.5	1.4	859	0.26	7.6	1.2	10.0	1.3	4.6	2.2	−0.8	3.3	0.30	7
23/F‡	12.7	19.2	18.6	2.2	1287	1.10	8.8	1.5	10.0	0.5	0.6	7.9	−5.9	8.6	0.15	3
24/F	13.3	18.9	13.1	1.0	39	0.32	10.2	1.2	11.5	3.0	0.7	6.5	−6.3	14.7	0.30	3
25/M	14.2	14.9	20.1	1.2	597	0.41	9.7	1.4	11.5	0.5	3.4	3.0	−2.2	4.0	0.30	7
26/M	14.3	16.1	12.3	2.0	917	0.60	9.0	1.6	12.0	0.5	3.3	4.4	−2.1	4.2	0.30	7
27/M	14.9	19.1	15.8	2.4	1558	0.35	11.2	1.8	11.5	1.5	5.3	5.8	0.4	4.0	0.30	7
Mean ± SD . . .	11.7 ±2.7	16.4 ±1.9	16.4 ±5.2	1.7 ±0.5¶	962 ±464‖	0.49 ±0.27#	7.9 ±2.4	1.3 ±0.3	9.2 ±2.5	1.2 ±0.9	3.4 ±1.6	4.3 ±2.2	−2.6 ±2.1	5.5 ±3.8	0.27 ±0.06	5.0 ±2.1
Group 3																
28/F†	9.9	13.1	41.9	3.1	2333	0.73	5.6	0.8	6.8	0.7	4.1	1.5	−2.0	1.9	0.49	3
29/M†	10.3	15.8	23.5	3.4	2777	0.49	6.9	1.2	6.5	. . .	3.0	3.7	−3.3	. . .	0.30	7
30/M†	10.7	12.7	15.2	4.0	3288	1.16	6.8	0.8	10.0	1.5	4.6	1.5	−0.8	2.3	0.30	7
31/F	10.7	16.3	35.0	2.7	. . .	1.72	8.2	0.5	13.5	0.0	1.5	1.9	−2.6	2.0	0.30	7
32/F†	11.9	14.6	17.9	3.2	3025	2.39	6.9	1.4	8.3	1.7	3.2	5.9	−2.9	7.3	0.25	7
33/M‡	12.7	16.4	13.5	3.4	2147	0.43	8.8	1.0	8.5	0.5	2.8	2.7	−3.4	3.6	0.15	6
34/F†	13.0	14.2	17.6	5.5	5646	1.86	8.8	1.5	12.0	. . .	4.6	3.2	−3.4	. . .	0.30	7
35/M	14.3	18.9	21.2	2.8	2408	1.22	9.6	2.2	12.0	2.0	4.6	6.2	−0.5	1.6	0.19	3
36/M‡	14.8	16.0	21.1	6.3	5147	0.49	9.4	1.0	11.5	0.0	3.3	3.1	−2.3	4.2	0.15	3
37/M	15.5	17.9	23.2	4.4	3701	1.13	10.2	1.7	11.0	1.6	5.9	2.5	1.3	1.6	0.30	7
38/M	16.2	16.7	17.9	3.3	. . .	0.18	11.3	2.0	13.0	. . .	0.7	9.0	−5.7	. . .	0,30	7
Mean ± SD . . .	12.7 ±2.2	15.7 ±1.9	22.5 ±8.6	3.8 ±1.1	3386 ±1246	1.07 ±0.69	8.4 ±1.7	1.3 ±0.5	10.3 ±2.4	1.0 ±0.8	3.5 ±1.5	3.7 ±2.3	−2.3 ±1.8	3.1 ±2.0	0.27 ±0.09	5.8 ±1.9

*CA indicates chronologic age; BMI, body mass index; GH, growth hormone; AUC, 24-hour area under the curve; IGF-I, insulin-like growth factor–I; Pre, pretreatment; HA, height age; BA, bone age; HVz, height velocity *z* score; and SC, subcutaneous.

†Tanner stage I throughout the study period.

‡Tanner stage I when somatropin (human growth hormone) therapy started.

§Group 1 vs group 2, $P<.001$.

‖Group 1 vs group 3, $P<005$.

¶Group 2 vs group 3, $P<.0001$.

#Group 2 vs group 3, $P<.05$.

bone age (BA) were growing 5.7 and 5.0 cm/y, respectively. Ten patients remained prepubertal (Tanner breast/genitalia) throughout the study period. One girl (patient 12) advanced to Tanner stage III during treatment. Ten patients had idiopathic hypopituitarism with one or more hormones replaced; two children (patients 2 and 15) had received cranial irradiation; and one each had schizencephalic porenchelaphy (patient 10), pituitary hamartoma (patient 8), craniopharyngioma (patient 12), status postmeningitis (patient 13), and unclassified central nervous system disease (patient 9).

Group 2

The peak GH response to any one provocative test was 10 μg/L, and the mean 24-hour GH concentration (mean 24-hour GH) was 2.5 μ/L or less ($n=10$, seven males and three females); the pre-HV was 4.0 cm/y or less, with four exceptions as follows: patients 18 and 22, prepubertal boys growing 4.3 and 4.6 cm/y, respectively; patient 20, a prepubertal girl growing 4.7 cm/y; and patient 27, a pubertal boy with an inappropriately low plasma IGF-I concentration for BA and pre-HV of 5.3 cm/y. Four patients remained prepubertal throughout the study period. One male (patient 22) advanced to Tanner stage II, and one female (patient 23) progressed to Tanner stage IV. One patient (patient 21) had received cranial irradiation. Two (patients 18 and 24) had "empty" sella turcica by intracranial imaging.

Group 3

The peak GH response to any provocative test was 10 μg/L or greater, and the mean 24-hour GH was greater than 2.5 μg/L ($n=11$, seven males and four females). These short children displayed a range of pre-HV; five remained prepubertal throughout the study period; one male (patient 33) advanced to Tanner stage II, and another (patient 36) progressed to Tanner stage III; two patients (patients 28 and 35) had empty sellae (one with Noonan's syndrome); one each had Russell-Silver syndrome (patient 30), status postmeningoencephalitis with seizures (patient 38), and a cyst of the septum pellucidum (patient 31).

Treatment

Patients were treated with biosynthetic recombinant somatropin at a dosage of 0.15 to 0.30 mg/kg per week (one patient received 0.49 mg/kg per week) that was injected subcutaneously three to seven times weekly per the preference of the attending endocrinologist. Thirty-six children received somatrem (methionyl human growth hormone); two patients received natural-sequence somatropin. The children were examined every 3 months.

Assays

The GH response was measured with a polyclonal double-antibody radioimmunoassay,[12] with interassay and intra-assay coefficients of variation of 13.7% and 7.8%, respectively. The IGF-I was measured with reagents obtained from the Nichols Institute, San Juan Capistrano, Calif, with interassay and intra-assay coefficients of variation of 13.6% and 8.7%, respectively. Skeletal maturation was assessed by the method of Greulich and Pyle.[13] Pubertal staging was assessed by the method of Tanner,[14] utilizing breast development for girls and genital development for boys.

Statistics

The data were examined by one- and two-way analyses of variance, the independent t test, and multiple linear regression analysis. Scheffe's test was used to minimize the rate of type I errors; however, because of the number of comparisons across variables, some inflation of risk for type I errors may have been introduced. Data are expressed as mean ± SD, except when so indicated. A P value of .05 or less was considered to be significant. By using cluster analysis,[15] a curve for the 24-hour GH secretory pattern was established, and the 24-hour area under the curve (AUC) was calculated and expressed as micrograms per liter per minute. The AUC was not calculable by this method if four or more data points (of 73) were missing. The HV SD scores (z scores), based on chronologic age (CA; HVz CA) and BA (HVz BA), were calculated based on normal data provided by Smith.[16]

RESULTS

Clinical findings in the three patient groups are presented in the Table. At onset of somatropin therapy, the three groups were similar in CA, body mass index, midparental height (data not shown), height age, BA, pre-HV (which was established over a mean observation period of 11.1 months [range, 4.5 to 30 months]), and pre-HVz. The mean duration of treatment was 12.6 months (range, 12.0 to 15.0 months), 12.5 months (range, 11.5 to 14.0 months), and 12.5 months (range, 11.5 to 14.0 months) for groups 1, 2, and 3, respectively.

By selection, the mean 24-hour GH was significantly greater in group 3 children (3.8 ± 1.1 μg/L) than that in groups 1 (1.7 ± 0.6 μg/L) and 2 (1.7 ± 0.5 μg/L) ($P<.0001$ for both groups). The AUC was significantly greater in group 3 children compared with groups 1 and 2 ($P<.0001$ for both groups). The correlation between the mean 24-hour GH and AUC was high ($r=.96$, $P<.0001$). The mean peak GH response to stimulation was greater in group 3 (22.5 ± 8.6 μg/L) and group 2 (16.4 ± 5.2 μg/L) children compared with group 1 (5.8 ± 2.6 μg/L) ($P<.0001$ and $P<.001$, respectively). Plasma IGF-I concentrations were higher in group 3 patients (1.10 ± 0.69 U/mL) compared with group 1 (0.40 ± 0.24 U/mL, $P<.005$) and group 2 children (0.49 ± 0.27 U/mL, $P<.05$). The plasma IGF-I concentration correlated with the mean 24-hour GH ($r=.5$, $P<.005$) and with the AUC ($r=.65$, $P<.0001$).

After 1 year of somatropin therapy, there were no differences in post–height age, post-BA, post-HV, post-HVz scores (data not shown), the incremental increases in HV (ΔHV), or ΔHVz scores among the three study groups. Compared with pretreatment growth rates, HV accelerated significantly after administration of somatropin in all three groups ($P\leqslant.0001$ for all groups). Compared with pretreatment values, HVz scores (HVz CA and HVz BA) also increased significantly after 1 year of somatropin administration (HVz CA: $P<.0001$, $P<.001$, and $P<.01$ for groups 1, 2, and 3, respectively [data not shown]; HVz BA: $P<.0001$, $P<.0001$, and $P<.0005$ for groups 1, 2, and 3, respectively).

In no group was there increased skeletal maturation relative to the increase in growth. The effect of somatropin treatment on epiphyseal maturation was assessed by determining the mean ratios for Δheight age/ΔBA). This ratio was 1.5 for group 1 patients, 1.6 for group 2 patients, and 1.1 for children in group 3.

In addition to the high correlation between AUC and the mean 24-hour GH previously noted, there were significant correlations between the peak GH response to stimulation and AUC ($r=.47$, $P<.005$) and the mean 24-hour GH ($r=.47$, $P<.005$). No correlation existed between the mean 24-hour GH and CA, body mass index, midparental height, pre–height age, pre-HV, pre-HVz, or ΔHV.

Negative correlations were found between ΔHV and pre-HV (Fig 1; $r=-.67$, $P<.0001$), between ΔHV and

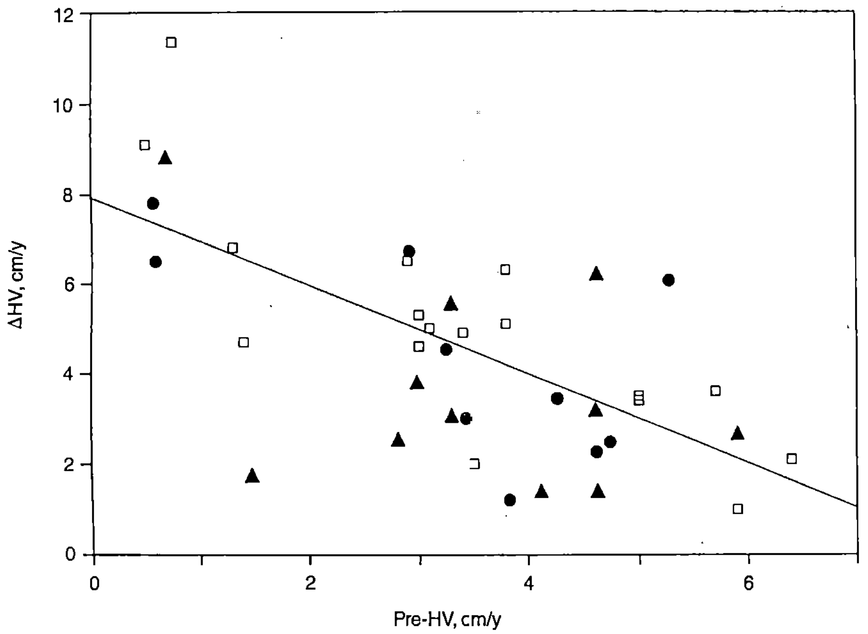

Fig 1.—Incremental change in height velocity (ΔHV) during 1-year administration of somatropin (human growth hormone) compared with pretreatment height velocity (pre-HV) ($r = -.67$, $P < .0001$). Open squares indicate group 1; closed circles, group 2; and closed triangles, group 3.

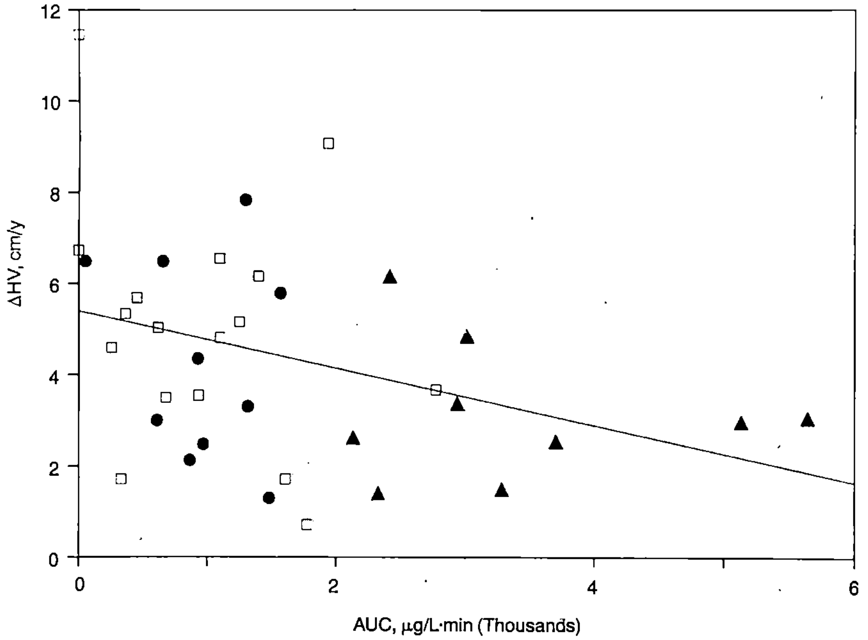

Fig 2.—Incremental change in height velocity (ΔHV) during 1-year administration of somatropin compared with area under the growth hormone curve (AUC) (endogenous growth hormone secretion) during 24 hours of measurement ($r = -.33$, $P < .05$). Open squares indicate group 1; closed circles, group 2; and closed triangles, group 3.

AUC (Fig 2; $r = -.33$, $P < .05$), and between ΔHV and peak-stimulated GH (Fig 3; $r = -.34$, $P < .05$). Log transformation of the data did not significantly modify the relationship (data not shown). By use of quadratic fit, these data did not demonstrate a curvilinear relationship (data not shown). A weak direct correlation existed between ΔHV and body mass index ($r = .34$, $P < .05$) but not between ΔHV and plasma IGF-I concentrations. There was no relationship between the ΔHV*z* CA and the mean 24-hour GH, AUC, or peak GH; the inverse relationships between ΔHV*z* BA and the mean 24-hour GH, AUC, and peak GH were weakly significant ($r = -.40$, $r = -.38$, and $r = -.35$, respectively; $P < .05$ for all groups).

After 12 months of therapy, there were no differences in the mean total weekly dosage of somatropin received by the three groups (Table); however, the mean frequency of injections per week was significantly greater in group 3 compared with group 1 (5.8 ± 1.9 vs 3.9 ± 1.7; $P < .05$). There were no correlations between ΔHV or ΔHV*z* and the dosage or frequency of administration of somatropin or significant differences among the three groups in mean ΔHV related to the dosage and frequency of administration of somatropin, as examined by two-way analysis of variance.

COMMENT

Other investigators have demonstrated improved growth rates in somatropin-treated short children without classic GH deficiency.[2-6,7,8] Kaplan[6] reported that 42% of normal short children (normal GH secretion in response to provocative stimuli) maintained an accelerated increment in HV of 2.0 cm/y or greater compared with pre-HV during 2 to 6 years of somatropin therapy. Endogenous GH secretion was not studied in these patients. The present investigation attempted to identify short children with "normal" GH secretion based on the results of provocative *and* physiologic studies, thus allowing the study of "short normal" patients.

Several workers[9,11,17-21] have reported studies of endogenous 24-hour GH secretion in short children with normal provoked GH secretion who were later treated with somatropin. Chalew et al[18] studied 11 poorly growing children with normal GH responses to provocative agents but "low" endogenous GH secretions, as assessed by integrated concentrations of GH throughout 24 hours. After 8 months of treatment, the mean incremental increase in HV was 3.2 cm/y. Albertsson-Wikland[19] reported that 17 of 18 prepubertal short normal children had an increase in HV of of 2.0 cm/y or greater during somatropin administration. Unlike the present study, that investigation recorded no relation-

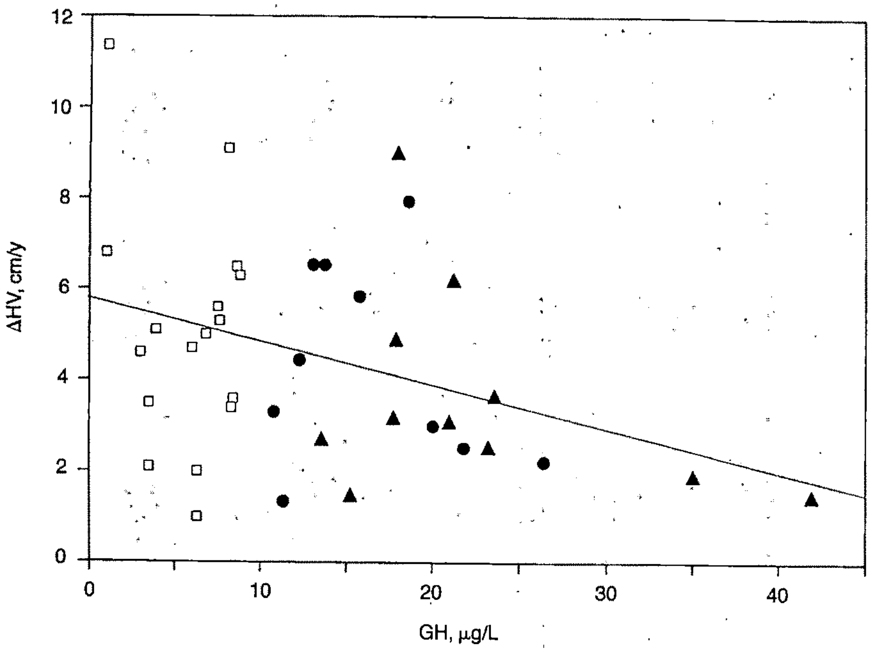

Fig 3.—Incremental change in height velocity (ΔHV) during 1 year of somatropin (human growth hormone) therapy compared with peak serum growth hormone (GH) concentration after a provocative agent ($r = -.34$, $P<.05$). Open squares indicate group 1; closed circles, group 2; and closed triangles, group 3.

ship between the peak-stimulated GH response and ΔHV, between peak GH and the 24-hour GH secretion (AUC over baseline), or between the pretreatment growth pattern and the response to somatropin administration. Hindmarsh and Brook[20] demonstrated increased HV*z* scores after somatropin therapy in 16 short prepubertal children who secreted adequate GH both endogenously and in response to pharmacologic stimuli. The results of the present study confirmed these data and demonstrated a significant relationship between the absolute ΔHV, as well as the ΔHV*z* BA, and parameters of endogenous GH secretion. These investigators[21] had previously reported a positive, nonlinear (asymptotic) relationship between pre-HV*z* scores of short normal children and the amount of GH secreted during 24 hours; poorly growing children secreted less GH. However, our data did not reveal a relationship between pre-HV or pre-HV*z* and AUC for GH secretion or the mean 24-hour GH. Recently, Lin et al[22] found no correlation between the mean pooled 24-hour GH concentration and pretreatment growth rate or between the mean pooled 24-hour GH and change in growth rate after 6 months of somatropin therapy; they too noted a negative correlation between ΔHV and pre-HV in somatropin-treated short children. Present data agree with those observations and those of Albertsson-Wikland[19] of an inverse relationship between ΔHV and endogenous GH secretion expressed as the AUC.

Attempts have been made to predict which children will benefit from exogenous somatropin with accelerated HV. The results of the present study confirm prior observations that patients who grow more slowly experience a greater acceleration in growth rate during somatropin therapy than do more rapidly growing short children. At present, this seems to be the best way to select children for a trial of somatropin therapy. As derived from Fig 1, 88% of short children who were growing 2.0 cm/y or less increased their HV after initiation of somatropin; 94% of those children who were growing between 2 and 4 cm/y increased HV by 2.0 cm/y or greater after somatropin therapy. In the children who were growing greater than 4.0 cm/y, 79% increased HV by 2.0 cm/y or greater during somatropin administration.

The present data also show that patients with higher endogenous 24-hour GH secretion, as reflected by the AUC (but not the mean 24-hour GH), responded less well to exogenous somatropin. Similar to the data of Hindmarsh and Brook[20] and others, the present study shows that increased height was not at the expense of excessive advance in skeletal maturation.

Interestingly, the present data reveal an inverse relationship between the peak GH response to provocative agents and ΔHV. This correlation was similar to that between AUC and ΔHV. Corroboration from other studies is necessary to confirm the implications of this finding.

CONCLUSION

Preheight velocity remains a vital factor in determining the response to somatropin therapy; in the majority of poorly growing children, despite their GH secretory dynamics, HV increases during the first year of somatropin therapy. Long-term follow-up will be necessary to determine if final stature is ultimately increased in these and other similarly treated short children. Recently, Kaplan and Grumbach[23] have reported that only 13% (3/24) of non–GH-deficient children treated with somatropin had an increase in final height greater than 2.5 cm over initial height prediction. The optimal dosage and frequency of administration of somatropin to non–GH-deficient patients were not determined in this study or in the present data. Further work, including risk-cost/benefit ratio analysis, is required to determine the optimal dose and frequency of somatropin to those children below the first percentile in stature, growing less than 4.0 cm/y who do not have classic GH deficiency.

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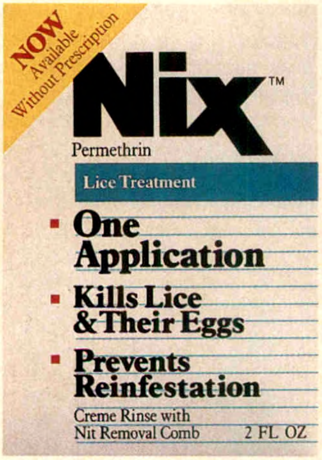

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Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia, Pa
Harold Levine, MPA, Galveston, Tex
Barbara Starfield, MD, Baltimore, Md
Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*We think that we are offering the best possible training for our residents, but how is that measured? How about asking our graduates how the training prepared them? Taras and Nader report such an evaluation, and the results are revealing. See how this applies to your program.*—H.D.A.

Ten Years of Graduates Evaluate a Pediatric Residency Program

Howard L. Taras, MD, Philip R. Nader, MD

• Ten years of graduates (1979 through 1988) from a pediatric residency program with a primary care track were surveyed for their perceived level of comfort gained in training for 28 different content/specialty areas of pediatrics and for their recommendations for increasing emphasis/time during residency for these areas. The response rate was 73%. The highest levels of comfort and fewest recommendations for increasing emphasis were for neonatal problems and health maintenance. The lowest perceived comfort levels and the most recommendations for increasing emphasis were for economics of pediatric practice and sports medicine/orthopedics. Graduates from the primary care track of the pediatric residency program expressed more comfort than did regular track graduates for some, but not all, areas of pediatrics emphasized in the primary care track program. Graduates of the first 5 years of study were not as comfortable with their training overall as were graduates from the most recent 5 years. This survey method and its results can provide useful information to medical educators faced with evaluation and revision of pediatric residency training programs.

(*AJDC.* 1990;144:1102-1105)

Evaluation of a residency program is essential to maintaining and improving the degree to which its educational goals are achieved. Although no single evaluative method alone is sufficient, surveying graduates of a training program is an essential component to the evaluation process.[1] Previous surveys of graduates from pediatric residency programs have proved to be useful for evaluating many facets of the training experience.[1,2] It has been shown that skills graduates of a residency program consider to be important in medical practice are not necessarily the same skills that they were prepared to perform.[3]

The health care needs of children and the goals of pediatric residency training have changed considerably since the last evaluation surveys were done. There has been an increasing trend toward ambulatory care of patients to decrease expensive inpatient management. Children with special medical needs have been deinstitutionalized and are now mainstreamed into regular school classrooms.[4] Behavioral and developmental aspects of pediatric practice, once termed the "new" morbidity,[5] are no longer new. Dealing with normal and aberrant behavior and development should have been integrated into the established domain of pediatric medicine. There are doubts about the extent to which residency programs with primary care tracks are increasing the quantity and competence of pediatricians in primary care careers.[6] Finally, as the economic nature of medical practice becomes complicated with numerous third-party payment options and as

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From the Department of Pediatrics, University of California, San Diego, La Jolla.

Reprint requests to the Division of General Pediatrics (H-664-A), University of California, San Diego Medical Center, 225 Dickinson St, San Diego, CA 92103 (Dr Taras).

corporations become increasingly involved with health care management, there may be a greater obligation for training programs to educate on the economics of practicing medicine. To investigate these issues, we conducted a survey of the last 10 years of graduates.

The University of California, San Diego, graduated its 10th year of pediatric trainees from its two-track residency program in 1988. Survey of the perceived comfort of our graduates for specific content areas of pediatrics is a part of an ongoing self-examination designed to evaluate our success in meeting new challenges placed on residency programs.

Physicians' self-rating of perceived comfort or competence is grounded in behavioral theory.[7] Social learning theory would suggest that physicians' behaviors are highly correlated with their perceived competence for a given task. As such, survey of physician self-rating of comfort may be indicative of their medical practices.

We studied the perceived competence/comfort of 10 years of graduates with the aim of answering several specific questions: (1) Does the overall perceived comfort with practicing pediatrics, using those skills learned in residency, differ between early and recent graduates? (2) In which content/specialty areas do graduates feel more comfortable and in which do they feel less comfortable? (3) Is comfort with specific content/specialty areas associated with enrollment in the primary care track?

METHODS

Pediatric residents who completed their training between 1979 and 1988 and who spent at least 2 consecutive years in the University of California, San Diego, pediatric residency training program were mailed a questionnaire. This population included graduates of the primary care track and of the regular track. All house officers had their own weekly primary care clinics, attended didactic sessions on primary care issues, and worked in the general pediatric clinics of the university-associated hospitals and at a local health maintenance organization. Graduates of the primary care track received additional training: they administered and supervised a hospital's primary care clinic and had 1 extra month of didactic and practical experience for learning, behavioral problems, developmental issues, and school and community health. Formal courses on practice management were not standard features of either track.

Addresses were available for 90% of graduates so that 82 questionnaires were sent. The questionnaire surveyed graduates on those elements of the program that were considered to be goals of our training, amounting to 28 different pediatric subspecialties and learning areas. Respondents rated their comfort on skills gained during residency for each element of the program on a seven-point scale (with 1 indicating most comfortable and 7 indicating not prepared) and their recommendation to increase the emphasis or time spent during residency on that topic on another seven-point scale (with 1 indicating no need to increase and 7 indicating greatest need). Analyses were conducted on all responses using the SPSS-X statistical package.[8]

RESULTS

Sixty of 82 graduates returned completed questionnaires (73% response rate). Nonrespondents were evenly distributed among all 10 graduating years. Seventy-one percent of the respondents

Table 1.—Mean ± SD Responses

	Comfort With Skills Gained During Residency	Recommendation for Increased Emphasis/Time During Residency
	Very Comfortable 1 2 3 · Little Uneasy 4 5 · Not Prepared 6 7	No Need to Increase 1 2 3 · Great Need to Increase 4 5 6 7
Normal newborn problems	1.52 ± 0.72	2.05 ± 1.46
Intensive care–neonatology	1.60 ± 0.74	1.63 ± 1.16
Health maintenance (immunizations, anticipatory guidance, screening tests, accident prevention)	1.71 ± 0.98	2.04 ± 1.43
Genetics and dysmorphology	2.03 ± 0.84	2.23 ± 1.40
Intensive care–pediatric	2.15 ± 1.02	2.53 ± 1.56
Infectious disease	2.20 ± 1.35	2.24 ± 1.50
Respiratory problems	2.27 ± 0.89	2.52 ± 1.50
Nutrition/feeding	2.47 ± 1.20	2.68 ± 1.34
Nephrology/urology	2.52 ± 0.92	2.65 ± 1.54
Metabolic disorders	2.76 ± 1.35	2.56 ± 1.55
Trauma and emergency	2.78 ± 1.47	3.03 ± 1.75
Allergy/immunology	2.92 ± 1.20	3.60 ± 1.66
Hematology	2.93 ± 1.31	3.05 ± 1.72
Cardiology	2.95 ± 1.33	3.35 ± 1.75
Oncology	2.98 ± 1.18	2.79 ± 1.69
Neurology	3.07 ± 1.03	3.53 ± 1.73
Gastroenterology	3.12 ± 1.15	3.26 ± 1.71
Ear, nose, and throat	3.12 ± 1.19	3.62 ± 1.52
Endocrinology	3.20 ± 1.35	3.65 ± 1.65
Behavior problems	3.41 ± 1.30	4.04 ± 1.69
Developmental delay and school problems	3.63 ± 1.40	4.02 ± 1.62
Dermatology	3.73 ± 1.46	4.71 ± 1.53
Adolescent medicine	3.75 ± 1.55	4.05 ± 1.89
Ophthalmology	4.22 ± 1.41	4.30 ± 1.89
Community resources (drug programs, parent support groups, social services, public health resources)	4.73 ± 1.72	5.02 ± 1.68
Psychiatric disorders	4.80 ± 1.28	4.67 ± 1.35
Sports medicine/orthopedics	5.02 ± 1.43	5.19 ± 1.42
Economics of pediatric practice	5.78 ± 1.60	5.43 ± 1.70
Total average	3.12 ± 0.58	3.43 ± 0.91

were male. Among the 60 respondents, 10 were in fellowship training during the time of the survey. Among those not in training, 37 (74%) were either practicing primary care pediatrics (general or adolescent) or subspecializing in developmental/behavioral pediatrics. The other 13 (26%) practiced in non–primary care subspecialties. Three respondents practicing emergency medicine were included in the latter group. Gender and year of graduation were not significantly associated with career choice. Eight (16%) of the 50 respondents who were not in fellowship programs were practicing part-time, six of whom were female and five of whom were in office-based practices. Thirty-eight percent of female respondents practiced only part-time compared with 6% of male respondents ($P<.001$).

Ratings varied from 1.52 (most comfortable) in "normal newborn problems" to 5.78 (least prepared) for "economics of pediatric practice." The average scores for each learning area surveyed are listed in order of decreasing comfort in Table 1.

The highest recommendations for an increase in emphasis or time during residency were given for areas of pediatrics in which graduates felt least comfortable (Table 1). There were no significant differences between the "recommendation" score and the "comfort" score when analyzed separately for each of the 28 different learning areas.

Primary Care Track vs Regular Track

Among all graduates not in fellowship training, 83% of primary care track and 69% of regular track graduates chose primary care or developmental/behavioral careers. These figures are not significantly different. Primary care track graduates felt more comfortable with the skills they learned in residency for dealing with "health maintenance" and "developmental delay and school problems" (Table 2). There were no significant differences in comfort for other surveyed learning areas.

Recent vs Early Graduates

Respondents were almost evenly distributed between the initial five (n = 29) and the most recent five (n = 31) graduating classes. In the program as a whole, recent graduates reported more comfort with skills gained during residency than did early graduates. In the individual learning areas, this was significantly true for "health maintenance," "respiratory problems," "cardiology," "gastroenterology," "adolescent medicine," and "community resources" (Table 3). Early graduates recommended more time/emphasis during residency for "developmental delay and school problems" than did recent graduates.

COMMENT

Our 73% response rate to the survey confirms that the use of graduates to evaluate a program is feasible. It may indicate that most graduates regard their own perspectives to be valid and important information for residency program evaluation.

A high proportion of female graduates are not in fellowship training and responded that they do not practice full-time. No data were collected on how

Table 2.—Mean Response by Residency Track for Items Having Significant Differences*

	Track		
	Primary Care (n = 18)	Regular (n = 42)	Significance, *P* Value
Health maintenance (immunizations, anticipatory guidance, screening tests, accident prevention)	1.39	1.88	.03
Developmental delay and school problems	2.95	3.95	<.01

*Values represent "comfort with skills," rated on a scale from 1 (very comfortable) to 7 (not prepared).

Table 3.—Mean Responses by Year of Graduation for Items Showing Significant Differences

	Comfort With Skills Gained During Residency*					
	1978-1984 (n = 29)	1985-1988 (n = 31)	Significance, *P* Value	1978-1984	1985-1988	Significance, *P* Value
Health maintenance (immunizations, anticipatory guidance, screening tests, accident prevention)	2.60	1.45	<.04	. . .	. . .	. . .
Respiratory problems	2.64	1.94	.002	. . .	. . .	. . .
Cardiology	3.48	2.45	.002	. . .	. . .	. . .
Gastroenterology	3.52	2.74	<.008	. . .	. . .	. . .
Developmental delay and school problems				4.60	3.55	<.02
Adolescent medicine	4.17	3.35	<.04	. . .	. . .	. . .
Community resources (drug programs, parent support groups, social services, public health resources	5.34	4.16	<.007	. . .	. . .	. . .
Average of all 28 learning areas	3.30	2.96	<.02	. . .	. . .	. . .

*"Comfort with skills" was rated on a scale of 1 (very comfortable) to 7 (not prepared).
†"Recommendations" were rated on a scale of 1 (no need to increase) to 7 (great need to increase).

permanent this situation is or on the

reluctance to devote precious training

nance" and "developmental delay and

[redacted]

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sent to all pediatric residents and fellows and to any pediatric staff member who had contact with the pediatric residents and fellows. The questionnaire consisted of two parts.

Part A

With the use of a Likert Scale of 1 to 5, the pediatric residents and staff were asked to rate the importance of 40 different qualities that might contribute to learning in clinical pediatrics. By using this method, the most important perceived qualities of effective teaching could be obtained for the whole group, as well as for a comparison between staff and residents using a Student's t test.

Part B

The pediatric residents and staff were asked to rank five out of a list of 15 of the most important qualities of those teachers who stood out as excellent, either because they were recipients of awards for teaching excellence or they served as role models for teaching excellence. The qualities of the excellent clinical teacher were obtained for the whole group, and comparisons were made between the staff and the residents with the use of a Student's t test.

RESULTS

Questionnaires were sent to and received from the following study population groups: faculty and staff, residents/fellows, postgraduate subjects, and subjects whose level of training was not indicated (Table 1).

Table 1.—Questionnaire Study Population

Study Group	Questionnaire Sent	Questionnaire No. (%) Received
Faculty and staff	**179**	90 (50)
Resident year		
I	18	7 (39)
II	17	11 (65)
III	23	14 (61)
IV/fellows	50	25 (50)
Postgraduate residents, total	**108**	57 (53)
Subjects whose level of training was not indicated	. . .	6
Total	**287**	153 (53)

Part A

Residents and staff were asked to indicate the importance of specific behaviors or teaching approaches of clinical teachers, as these contribute to the learning of clinical pediatrics. A Likert Scale was used with the following ratings: 1, most important for good clinical teaching and contributes significantly to facilitate learning of clinical pediatrics; 2, moderately important for good teaching and good teachers; 3, of some importance for good teaching; 4, of little importance for teaching; and 5, least important for teaching or to facilitate learning.

The mean and the SD of 40 different qualities and attributes were calculated, and Table 2 indicates the rank importance as perceived by the total group.

For the perceptions of the total staff and total residents/fellows, when the mean scores were compared with the use of a two-tailed Student's t test, only four characteristics were found to be statistically significantly different ($P<.05$), and only two were found to be of any importance: the staff ranked "Approaches teaching/learning with enthusiasm . . . " higher than the residents/fellows, ie, rank of 1 and mean of 1.33 vs rank of 6 and mean of 1.54; the staff ranked "Able to stimulate intellectual curiosity and self-directed learning . . . " higher than the residents/fellows, ie, rank of 6 and mean of 1.51 vs rank of 18 and mean of 1.84.

Part B

The same question was asked in a different fashion. Staff and residents were asked to rank the five most important characteristics of an excellent teacher, a teaching excellence award winner, or a colleague or a teacher whom they had admired as being outstanding. A scoring system was used that would take into account both the frequency of the choice of the qualities and the ranking of the qualities, and from this, a percentage of the maximum score was calculated.

When the different groups were compared, there was surprisingly little difference. Only the ranking of one quality was found to be statistically significant ($P<.05$): the total staff ranked "An excellent role model . . . " with a rank of 3 and a percent maximum score of 39 higher than the total residents/fellows (rank of 6 and percent maximum score of 24) (Table 3).

COMMENT

Given that the goal of teaching is to promote learning and to help students acquire the knowledge, clinical skills, behaviors, and attitudes that are important for the practice of medicine, it seems obvious that the only valid way to evaluate teaching is in terms of how much students actually learn as a result of the teaching. Thus, the best teacher is the one whose students learn the most, and the worst teacher is the one whose students learn the least. However, in clinical medicine especially postgraduate medical education, there are many variables that affect student learning, including the students' abilities, the students' previous training, different teaching/learning situations, and different teachers. It is almost impossible to use student performance and achievement at a postgraduate level to assess teacher effectiveness.[17] Dr *A.* is our best junior resident in pediatrics, and Dr *A.* spent 1 month on ward 6C where I am the attending physician. Does this mean that I am one of the best clinical teachers? It would be impossible to assess my contribution as a teacher to Dr *A.*'s being our best pediatric resident. Instead, more commonly, evaluations of teaching make use of the student's perception of learning. It would be reasonable and fair to ask Dr *A.* how much he or she felt he or she had learned during his or her month on ward 6C, and how would he or she compare my teaching as it contributed to his or her learning with other teachers he or she has met. Student ratings of teachers are widely used and are as reliable and valid as any other measure of teacher effectiveness. There is a weak to moderate positive correlation between student ratings of teachers and actual student achievement, that is, students who rate their teachers as being effective do show higher standards of achievement.[13,17] Our study used this approach as residents and staff were asked their perceptions of what characteristics of teachers have helped them to learn clini-

[redacted]

Table 3.—The Excellent/Most Outstanding Teacher

	Total	Staff	Residents/Fellows
	% Maximum	% Maximum	% Maximum

[redacted]

students have been “seduced” into be-

lecture to two or three residents while

provided a financial grant for this study.

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choice required balanced information. Two hours of raw footage was eventually edited to the final version.

Subjects

A number of screenings of the film were held before audiences assembled for other purposes. These audiences included genetic counselors, nurses, and other medical professionals meeting for continued medical education purposes and parents of children with Down syndrome attending workshops and meetings. The same film was introduced to each audience as a teaching film about parenting a child with Down syndrome. Immediately after the film and prior to any discussion, viewers were asked to complete a three-page anonymous evaluation form requesting demographic information, impressions of the film, beliefs about prenatal diagnosis, and predicted behavior in response to several scenarios. The evaluation was organized in a Likert Scale format with responses of 1, 2, 3, 4, and 5 signifying the respondent's degree of disagreement (1) or agreement (5) with each statement. An area for narrative comment was also provided.

The evaluation responses from the three largest, distinct groups (parents, genetic counselors, and nurses) were compared. Responses from members of other professional categories were too few to create additional groups and too diverse to combine. Because all the nurses and most of the members of the other two groups were female, the responses of male subjects were excluded for the purpose of this study. A total of 155 evaluation forms were completed and returned. Although the actual attendance at each meeting was not recorded, each audience was small enough to determine that nearly all viewers completed an evaluation form. A diverse assortment of medical professionals accounted for 44 responses that were excluded from this study. The 5 male respondents among the genetic counselors and the 9 male respondents among the parents were also excluded. The remaining 97 evaluation forms were reviewed. The three respondent groups included 36 mothers, 29 genetic counselors, and 32 nurses (Table 1). All the nurses and mothers and all but 5 of the genetic counselors lived in New England. The mothers and both groups of professionals were of similar ages, educational levels, and socioeconomic backgrounds, and the nurses were all obstetric care nurses. Data about parenthood among the professionals were not gathered. None of the nurses or genetic counselors had personal, as opposed to professional, experience with Down syndrome.

Table 1.—Composition of Study Groups

Group	No.	Mean Age, y (Range)	Mean Age of Children With DS, y (Range)*
Mothers	36	37.3 (26-60)	7.5 (0.5-29)
Nurses	32	36.1 (20-58)	...
Genetic counselors	29	35.7 (25-51)	...
Total	**97**	36.4 (20-60)	...

*DS indicates Down syndrome.

Table 2.—Usefulness of Film*

Statement	Mothers	Genetic Counselors	Nurses
High educational value	91†	29	56†
High emotional impact	83	64	72
Appropiate for			
Medical professionals	92†	56	84
Parents of fetus with DS	72†	15	50‡
Parents of child with DS	86†	32	72†
Film stimulates discussion	89†	52	62
Film helpful to me	67†	14	66†
Film changed my attitudes	14	10	19

*Values represent the percent who agree with the statement.
†Significant difference vs genetic counselors, $P<.005$.
‡Significant difference vs genetic counselors, $P<.05$.

Table 3.—Accuracy of Film*

Statement	Mothers	Genetic Counselors	Nurses
Portrays parental attitudes	89†	14	41‡
Portrays medical attitudes	78†	10	23
Portrays genetic counseling	70†	4	13

*Values represent percent who agree with the statement.
†Significant difference vs genetic counselors, $P<.005$.
‡Significant difference vs genetic counselors, $P<.05$.

Due to the relatively small sample size, the data were dichotomized on the basis of the mean Likert Scale response of the entire population. The sum of all response choices of all subjects was divided by the total number of responses, resulting in a mean response of 3.43. As a result, responses of 1, 2, and 3 were recoded as "disagree" (with the statement) and responses of 4 and 5 being recoded as "agree" (with the statement). Each of the responses was examined by three individual χ^2 analyses comparing each group with each of the remaining groups.

RESULTS

The percentages of each group in agreement with each statement on the evaluation form were calculated and compared. All three groups differed in some of their beliefs about the film and about prenatal diagnostic testing. The most dramatic differences were found between the mothers and the genetic counselors; the nurses' responses varied. For some items, the nurses' responses were similar to those of one of the other two groups, but for many items they occupied an intermediate position between the other groups.

Items on the evaluation form referring to the content of the film were divided into two categories. The first category included statements about the film's applicability to various audiences, its overall educational value and emotional impact, and its usefulness (Table 2). The second category included statements about the accuracy of the film's portrayal of parents, medical professionals, and genetic counselors (Table 3).

More than 90% of the mothers thought the film had high educational value and would be appropriate for use by professionals-in-training. Genetic counselors' responses differed signifi-

Table 4.—Beliefs About Genetic Counseling*

Statement	Mothers	Genetic Counselors	Nurses
Prenatal diagnosis useful for prevention of disability	47†	78	81
Need genetic counseling before amniocentesis	81†	100	81†
Need genetic counseling before MSAFP	72	86	72
Genetic counseling is unbiased	18‡	62	36

*Values represent percent who agree with the statement. MSAFP indicates maternal serum α-fetoprotein.
†Significant difference vs genetic counselors, $P<.05$.
‡Significant difference vs genetic counselors, $P<.005$.

Table 5.—Beliefs About Down Syndrome*

Statement	Mothers	Genetic Counselors	Nurses
Newborn information to parents of fetus with DS	81	56	63
Parents of fetus with DS should meet parents of child with DS	64	52	69
Parents of child with DS choose to abort later fetus with DS	8†	57	10†
Problems exceed benefits of having child with DS	6†	48	17‡

*Values represent percent who agree with the statement. DS indicates Down syndrome.
†Significant difference vs genetic counselors, $P<.005$.
‡Significant difference vs genetic counselors, $P<.05$.

Table 6.—Predicted Choices*

Statement	Mothers	Genetic Counselors	Nurses
I choose prenatal diagnosis	52†	93	70
I would abort fetus with DS	9†	46	29
I would abort fetus with fatal condition	49‡	79	55
I would abort any abnormal fetus (however minor)	6	12	13
I would never abort	34†	0	16

*Values represent percent who agree with the statement. DS indicates Down syndrome.
†Significant difference vs genetic counselors, $P<.005$.
‡Significant difference vs genetic counselors, $P<.05$.

cantly ($P<.005$), with only 29% finding high educational value and 56% indicating that professionals were an appropriate audience. Among the nurses, 84% believed that professionals were an appropriate audience, and 56% thought the film was of high educational value. Nearly 90% of the mothers thought the film would be useful to stimulate discussion, while only half of the genetic counselors agreed ($P<.005$).

The film's portrayal of parents was believed to be accurate by 89% of the mothers, 41% of the nurses, and only 14% of the genetic counselors. Nearly all the narrative comment added by the genetic counselors included complaints that the film's portrayal of parenting a child with Down syndrome was too positive. Seventy percent of mothers responded that the film provided an accurate view of genetic counseling, and 78% indicated that the film portrayed the attitudes of medical professionals fairly; less than 10% of the genetic counselors agreed. The nurses also differed significantly from the mothers on these statements.

The remainder of the evaluation form addressed beliefs about prenatal diagnosis, Down syndrome, and predicted behaviors in hypothetical situations involving prenatal testing. There were items about the timing and value of genetic counseling, the "burden" of a child with Down syndrome, choices parents would make in future pregnancies, and choices the viewer might make about prenatal testing and abortion (Tables 4, 5, and 6).

With notable exceptions, there was more agreement among the groups on the "beliefs and choices" statements of the evaluation form. Mothers were less positive about the usefulness of prenatal diagnosis in preventing birth defects than were the other two groups ($P>.05$). However, most members of all three groups agreed that genetic counseling before amniocentesis and before prenatal screening with maternal serum α-fetoprotein was desirable. A majority in each group believed that parents of a fetus with Down syndrome should be given the same information as parents of an affected newborn. While 62% of the genetic counselors felt that genetic counseling was unbiased, only 18% of the mothers agreed with this statement ($P<.005$).

Fifty-six percent of the genetic counselors predicted that parents of a child with Down syndrome would abort a subsequent affected fetus while only 8% of mothers and 10% of nurses agreed. Forty-eight percent of the genetic counselors believed that the problems outweigh the benefits of parenting a child with Down syndrome while only 6% ($P<.005$) of mothers and 17% ($P<.05$) of nurses agreed.

Concerning their own choices, 9% of the mothers predicted that they would abort a fetus with Down syndrome. Forty-six percent of the genetic counselors ($P<.005$) and 29% of the nurses ($P>.1$) predicted that they would choose abortion in the same circumstance. Finally, a significantly larger number of the mothers (34%) than the genetic counselors (0%) would never choose abortion under any conditions.

COMMENT

We presented a film showing parents discussing their experiences with Down syndrome to mothers of children with

Down syndrome, genetic counselors, and nurses and compared their reactions. Differences among these groups were found in several areas, reflecting differing beliefs and expectations about Down syndrome and about some genetic counseling issues.

The results of our study must be considered in light of obvious methodologic flaws relating to sample selection and sample size. Studies of attitudes in which voluntary responses are usually required always contend with this issue. We acknowledge that our film's audiences were not randomly selected, that we lack the means for a rigorous comparison of the three groups, and that we are uncertain of the number of respondents compared with the total number of viewers. However, we believe that the differences noted were sufficiently significant to stimulate thoughtful discussion, further investigation, and a review of the training of those providing genetic counseling and obstetric nursing services.

The genetic counselors in our study held a more negative view of the family life of a child with Down syndrome than the mothers or, in some cases, the nurses. The addition of a child with Down syndrome to a family is not a neutral event. Although the literature on the impact of such a child is full of conflicting conclusions, there is general agreement that unique stresses are involved.[10] The initial diagnosis of Down syndrome in a newborn, usually an unanticipated tragedy for families, may be accompanied by intense feelings of shock, grief, guilt, and despair.[11] The ensuing adjustment has been called a "values crisis" and is often a period of high risk for marital discord.[12] However, looking at the longer term, Gath[13] compared the families of 30 children with Down syndrome matched with the families of 30 "normal" children from birth to age 2 years and found no differences in the physical or emotional health of parents. A 6-year follow-up study of these groups demonstrated "few differences in the family lives of the two groups."[14] Feingold and O'Brien[15] reported a survey of 382 New England parents with backgrounds similar to those in our group. Eighty-nine percent stated that their child with Down syndrome had exceeded their expectations.[15] The vast majority of subjects of Feingold and O'Brien found that their child did not have a negative impact on family relationships. Marital and family conditions before the birth of a child with Down syndrome must be determined retrospectively in most cases, but some studies suggest that the impact of the child is determined by prior characteristics of the family.[16] Furthermore, recent improvements in supportive community resources may play a role in the determination of a positive family adjustment.[17]

Few published data exist about the actual choices made by parents of a child with Down syndrome confronted with a recurrence in a subsequent pregnancy. One study found that 48 (68%) of 71 mothers predicted that they would abort in the case of a future affected pregnancy.[18] However, others have found lower predicted rates. Elkins et al[19] found, in a survey of mothers of children with Down syndrome, that 50% of mothers opted for prenatal diagnosis in subsequent pregnancies. Of those having prenatal testing, about half would consider aborting an affected fetus, but none were actually confronted with the choice. Oetting and Steele[20] reported that only 17% of their group of parents of a child with Down syndrome availed themselves of prenatal diagnosis during the next pregnancy. Feingold and O'Brien[15] found that 42% of parents of a child with Down syndrome predicted that they would have amniocentesis in a future pregnancy, but only 13% would terminate an affected pregnancy. Furthermore, Feingold and O'Brien found that of 224 mothers of children with Down syndrome who had a subsequent pregnancy, 73% elected not to have amniocentesis.

Why do the genetic counselors in this study have a more pessimistic view of family life for a child with Down syndrome? First, selection bias may have influenced the mothers participating in the study. Mothers with more negative points of view may have been less likely to attend workshops and parent support group meetings where the film was screened. Second, the work experience of genetic counselors often involves contact with families during the intensely negative crisis of initial diagnosis and little longitudinal contact. As a result, genetic counselors see little of family adjustment and of positive outcomes. In the setting of prenatal diagnosis, genetic counselors deal almost exclusively with pregnant women who are considering prenatal testing and who may present with preconceived notions of terminating an affected pregnancy. Such patients may have more negative ideas about bearing a child with a disability than those pregnant women who do not seek prenatal testing. Third, the education of genetic counselors may come predominantly from members of their own or related professions whose experience has been similarly limited. A respected and recently revised medical genetics textbook[21] still refers to people with Down syndrome as "mongols" and contains such erroneous and negative statements as "50% die before age five years." Finally, some genetic counselors involved in the process of prenatal diagnosis may believe that its goal is a reduction in the birth incidence of Down syndrome (rather than offering choices to individual families). For example, at a recent meeting, Dr Sumner Yaffe of the Center for Research for Mothers and Children at the National Institute of Child Health and Human Development, Bethesda, Md, stated, "The Foundation [for Blood Research] has embarked on another prenatal screening program that has, and will play, a significant role in removing another significant cause of mental retardation—Down syndrome."[22] It may be difficult to reconcile a more positive view of Down syndrome with a personal belief in a policy of reduced birth incidence.

The suggestion that bias might play a role for professionals in the discrepant reactions to our film can also be made for parents. Parents have invested considerable time and emotional energy in the nurturance of their children with Down syndrome. However, bias among professionals, when it exists, may have more far-reaching impact. Bias may be overtly expressed, although this violates the genetic counseling tenet of "non-directiveness." A recent survey of physicians in southern France found that 78% favored termination of pregnancy in cases of Down syndrome and that 33% would voice their opinions to counselees.[23] Bias may also be unacknowledged or hidden and still influence services such as prenatal diagnosis. In an editorial comment about the use of bone marrow transplantation in children with Down syndrome for treatment of acute lymphoblastic leukemia,[24] Churchill[25] stated: "Prejudice need not be conscious to be present. Unintended bias against DS [Down syndrome] children can be all the more powerful for being unarticulated, especially among professionals who hold high ideals."

Ninety percent of the mothers in our study believed that the film *Down Syndrome—A Parental Perspective* was of high educational value, would be useful to stimulate discussion, and would be of value to the education of medical professionals. Perhaps the medical professionals dealing with the impact of disability on families require broader exposure to those families. Curricular changes are needed that include parents as valued experts and place students in their midst at home and in the community. Agencies providing genetic services need to respond to consumers of their services and to families affected by genetic conditions. The genetics curricula in medical schools need to make expanded use of presentations by parents and families. Medical genetics educators are developing guidelines that provide substantial attention to the issues of attitudes and communication skills.[26,27] These principles must guide the teaching of genetic service providers and the evaluation of their textbooks and other materials. Obstetric nurses have less exposure to Down syndrome than do genetic counselors, but the experience they have occurs during the critical period soon after the diagnosis in a newborn. For this reason, it is important that such nurses have some educational exposure similar to that proposed for genetic counselors.

The past decade has brought many changes to the prospects and life-styles of children with Down syndrome, who can expect to be nurtured in a loving family, to be afforded comprehensive and anticipatory health care, to receive an appropriate education, and to lead longer and more productive lives.[28] During this same decade, progress in prenatal medicine has led to safer and earlier prenatal diagnosis of Down syndrome. Identification of the majority of affected pregnancies is both technically and economically possible. It is important that these simultaneous developments not become contradictory or polarizing processes. The experience of families affected by Down syndrome bears valuable insights both for professionals providing prenatal genetic counseling and for expectant parents utilizing those services.

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This article is dedicated to the memory of Dorothy Whitmore, whose warm and cheerful spirit as a parent and advocate persists in those she touched.

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Transient Myeloproliferative Disorder of the Down Type in the Normal Newborn

Derry Ridgway, MD; Gerda I. Benda, MD; Ellen Magenis, MD; Leland Allen;
Gerald M. Segal, MD; Rita M. Braziel, MD; Robert C. Neerhout, MD

• Two infants with congenital nonlymphoblastic leukemia were discovered to have mosaicism for trisomy 21. Both infants achieved durable spontaneous remissions. Trisomy was apparently restricted to the leukemic clone and could be detected in neither phytohemagglutinin-stimulated peripheral blood cells or bone marrow in either patient nor in myeloid progenitor cells from the second patient after resolution of the transient myeloproliferative disorder. We conclude that spontaneous remission of congenital leukemia is not confined to infants with partial or complete systemic trisomy 21 but can occur in genetically normal newborns whose leukemic cells contain a third chromosome 21.

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The association of Down syndrome (DS) and congenital leukemia was first reported by Schunk and Lehman[1] in 1954. The majority of infants with DS with congenital leukemia will undergo a spontaneous and durable remission, while a minority will have progressive leukemia requiring therapy.[2] The syndrome of spontaneously resolving congenital leukemia, termed *transient myeloproliferative disorder* (TMD), occurs almost exclusively in infants with DS, or with mosaicism for trisomy 21. Patients with spontaneously remitting neonatal leukemia unassociated with trisomy 21 have been described,[3,4] but only a single such child maintained a long remission.[4] Both TMD[5-9] and leukemia[10] are known to occur in children with mosaic trisomy 21, and in all such patients the abnormal hematologic cells are derived from the trisomic fraction. Six newborns with TMD and mosaic trisomy 21 have been described,[5-9] including two[7,8] in whom the trisomic karyotype was apparently limited to the abnormal hematologic clone. We describe two additional newborns with TMD and mosaic trisomy 21 limited to the transient leukemic clone.

PATIENT REPORTS

PATIENT 1.—A 4.3-kg male neonate was born at term after an uncomplicated gestation. He was referred to Doernbecher Memorial Hospital for Children, Portland, Ore, at 12 hours of age because of a diffuse maculopapular rash involving the trunk and proximal extremities, hepatosplenomegaly, mild respiratory distress, and a blood analysis showing a hemoglobin value of 94 g/L, a platelet count of 295×10^9/L, and a white blood cell (WBC) count of 66×10^9/L, with 0.53 blast cells.

Examination revealed no stigmata of DS. During the first week of life, the rash became vesicular and then resolved, the organomegaly decreased, and respiratory support was limited to oxygen therapy by mask. A skin biopsy specimen showed a lymphoid infiltrate with no evidence of giant cells; bacterial and viral cultures of the skin biopsy specimen yielded no organisms. A bone marrow examination at 48 hours of age showed increased cellularity, with 0.63 blast cells. The blast cells stained negative for peroxidase, Sudan black B, and periodic acid–Schiff stains but positive for nonspecific esterase, which is consistent with the diagnosis of acute myelomonocytic leukemia. The blasts did not have surface immunoglobulin, terminal transferase (TdT), or a receptor for sheep erythrocytes. During the first 2 months of life, the WBC count gradually decreased, and blast cells were not seen in the peripheral blood after day 21. Morphologic examination of a bone marrow aspirate obtained at 8 weeks of age showed normal hematopoiesis and no evidence of residual leukemia.

Chromosome analysis of unstimulated bone marrow cells obtained on day 2 showed 19 of 21 cells to be 47,XY, +21 and 2 cells to be normal (46,XY) (Table). Eight of 21 phytohemagglutinin (PHA)-stimulated peripheral blood cells obtained at the same time were 47,XY, +21 and 13 were normal. Examination of bone marrow, peripheral blood, and cultured skin fibroblasts obtained at 8 weeks of age showed normal karyotypes in all cells. Peripheral blood karyotypes from both parents were normal. Chromosomes stained with quinacrine mustard revealed that the patient's normal cells contained one maternal and one paternal chromosome 21. The abnormal cells contained a single copy of the same paternal chromosome 21 and two identical copies of the same maternal chromosome 21, suggesting that the trisomic cell line was derived from a nondisjunction of chromosome 21 during mitosis, or that it was a de novo abnormality occurring after conception in a hematopoietic progenitor cell.[11] The child was most recently seen at the age of 5½ years. He remains clinically well, with normal peripheral blood cell counts, growth, and intellectual development.

PATIENT 2.—A 2.58-kg neonate was born by spontaneous vaginal delivery at an estimated gestational age of 32 weeks. Respiratory support was required in the delivery room, and the infant was transferred to the Neonatal Intensive Care Unit at Doernbecher Memorial Hospital for Children. Examination revealed no stigmata of DS. Hepatosplenomegaly was present. An initial blood analysis showed a hemoglobin value of 87 g/L, a platelet count of 92×10^9/L, and a WBC count of 92.4×10^9/L, with 0.45 blast cells. The early hospital course was complicated by seizures, cellulitis, sepsis, and a transient cardiomyopathy.

A bone marrow aspirate on day 5 showed increased cellularity, with myeloid and erythroid hypoplasia, decreased numbers of megakaryocytes, and 0.50 blast cells. The blast cells were histologically undifferentiated and were biphenotypic for both T-cell and myeloid lineage. Specifically, the cells were stained with immunofluorescent antibodies against MY7 (CD33, 72%), MY9 (CD13, 64%), B4 (CD19, 63%), and Leu-9

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From the Department of Pediatrics (Drs Ridgway, Benda, Magenis, and Neerhout), the Division of Hematology and Medical Oncology, Department of Medicine (Dr Segal), and the Department of Pathology (Dr Braziel), the Doernbecher Memorial Hospital for Children, and the Crippled Children's Division (Mr Allen), Oregon Health Sciences University, Portland, Ore.

Reprints not available.

(CD7, 71%) and were negative for TdT, MY4 (CD14), common ALL antigen (CD10), and the megakaryocyte antigens GPIB (CDw41) and GPIIB (CDw40).

The WBC count gradually decreased after the 10th day of life, and blast cells were not seen in peripheral blood after day 11. Platelet transfusions were required until day 21; platelet counts remained above 150×10^9/L after 3 weeks of age. Morphologic examination of bone marrow aspirates obtained at 14 and 18 weeks of age showed normal cellularity, normal maturation of myeloid and erythroid lineages, a relative lymphoid hyperplasia, and 0.05 to 0.10 blast cells. Surface marker analysis of these two specimens showed decreases to normal levels of the number of MY7-, MY9-, and Leu-9–positive cells. A population of cells positive for TdT (15%) and CD10 (66%) appeared during this interval. At 14 months of age, a bone marrow aspirate was morphologically normal and contained a residual population(s) of TdT-positive (7%) and CD10-positive (39%) cells.

Chromosome analysis of unstimulated marrow cells at 5 days of age showed all cells with 47,XY, +21 (Table). In contrast, chromosome analysis of PHA-stimulated peripheral blood from day 8 and cultured skin fibroblasts from day 19 were normal (46,XY). Trisomic cells in unstimulated marrow disappeared during the first 4 months of life. The patient remains clinically well and has normal blood cell counts, growth, and development at 1 year of age.

LABORATORY METHODS

In an attempt to delineate the extent of mosaicism in patient 2, karyotype analysis of cultured myeloid cells was performed. Low-density bone marrow mononuclear cells from marrow aspirate at 18 weeks were grown in tissue culture as previously described.[12] Myeloid colony growth was stimulated by recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) at a final concentration of 10^{-10} mol/L. Colonies (aggregates of 20 or more cells) were enumerated and harvested on day 13 of culture.

Cytogenetic evaluation of harvested cells was performed using a modification of the procedures described by Raskind et al.[13] In brief, 0.15 mL of demecolcine (Colcemid, 10 mg/L, GIBCO, Santa Clara, Calif) was layered onto the culture medium and the cultures were incubated for another 2 hours. The individual colonies (n=76) were then aspirated using a Pasteur pipette and pooled, suspended in 0.5 mL of warmed 0.075 mol/L potassium chloride, and gently mixed. Ten drops of fixative (methanol–glacial acetic acid, 3:1, vol/vol) was added and the cell suspension centrifuged at 1000 rpm for 7 minutes and resuspended in 2 mL of fresh fixative. Cells in fixative were dropped onto wet slides previously cleaned in 95% alcohol and air dried. Fifty G-banded metaphases were counted and analyzed and, from these, 3 were totally karyotyped.

Chromosomal Analysis of Two Patients With Transient Myeloproliferative Disorder*

Age	Tissue	Preparation	No. of Cells	Karyotype (No. of Cells)
Patient 1				
2 d	Marrow	Unstimulated	21	47,XY, +21 (19); 46,XY (2)
	Blood	PHA-stimulated	21	47,XY, +21 (8); 46,XY (13)
8 wk	Marrow	Unstimulated	3	46,XY (3)
	Blood	PHA-stimulated	100	46,XY (100)
	Skin	Fibroblast culture	40	46,XY (40)
Patient 2				
5 d	Marrow	Unstimulated	20	47,XY, +21 (20)
8 d	Blood	PHA-stimulated	40	46,XY (40)
19 d	Skin	Fibroblast culture	40	46,XY (40)
4 wk	Marrow	Unstimulated	20	47,XY, +21 (4); 46,XY (16)
14 wk	Marrow	Unstimulated	20	46,XY (20)
18 wk	Marrow	Unstimulated	50	46,XY (50)
	Marrow	GM-CSF–stimulated	50	46,XY (50)
14 mo	Marrow	Unstimulated	20	46,XY (20)

*PHA indicates phytohemagglutinin; GM-CSF, granulocyte-macrophage colony-stimulating factor.

RESULTS

The average number of colonies per 10^5 cultured bone marrow mononuclear cells was 72, within the normal range for our culture system. Seventeen colonies were harvested onto glass slides and stained with Wright-Giemsa or butyrate esterase stains or both. Thirteen of those colonies were of granulocyte type and showed maturation beyond the blast stage. Three colonies were of monocyte-macrophage lineage, and one colony contained both granulocytes and macrophages.

As shown in the Table, the 50 G-banded metaphases from GM-CSF–stimulated myeloid colonies were all 46,XY. The three karyotypes prepared from those cells were normal.

COMMENT

The natural history of congenital leukemia in the cytogenetically normal newborn resembles that of leukemia in older persons in being nearly universally lethal if left untreated. In the infant with phenotypically evident DS, however, the likely outcome of an illness resembling congenital leukemia is spontaneous recovery. For that reason, antileukemic therapy is generally withheld unless and until the clinical course makes it clear that the child does not have TMD.

Nine phenotypically normal infants, including the two from Doernbecher Memorial Hospital for Children, have been described with TMD.[4-9] Chromosome analysis of eight infants, performed as part of the initial evaluation of leukemia, revealed mosaicism for trisomy 21. In each instance, the apparently malignant cell line was part of the trisomic clone. The self-limiting nature of congenital leukemia in some patients with DS appears to be related to the presence of the extra chromosome 21 in the "leukemic" clone since the association between an extra chromosome 21 and the possibility of spontaneous remission extends to congenital leukemia occurring in the phenotypically normal infant. This limiting role of the extra chromosome 21 is paradoxical, since the increased incidence of leukemia at all ages in DS has been attributed directly to the extraneous chromosome.[10,14]

The extent of mosaicism in the eight genetically mosaic, phenotypically normal infants with TMD was variable. In four, the trisomic clone extended beyond the abnormal hematologic cells. In the children described by Brodeur et al[9] and Heaton et al,[6] mosaicism was observed in PHA-stimulated peripheral blood cells and in skin fibroblasts. In the latter instance, trisomic cells were also noted among fibroblasts cultured from bone marrow aspirate. In both of these reports, in the child described by Weinberg et al,[5] and in the first child described by Seibel et al,[8] the trisomy observed among PHA-stimulated peripheral blood cells persisted long after the apparent resolution of the TMD (100 days, 194 days, 31 months, and 5 years, respectively). In contrast, the second patient described by Seibel et al,[8] the patient described by Hanna et al,[7] and the two patients described herein never showed trisomy beyond the hematopoietic compartment and had no detectable trisomy after the resolution of TMD. The first four neonates had trisomy 21 mosaicism in the usual meaning of the term, although the trisomic clone was ultimately quite small. The latter four patients appear to have had transient mosaicism, in the sense that older patients with cytogenetically abnormal leukemia have mosaicism until their leukemia is eradicated by therapy.

The concept that the trisomic cell line might be entirely absent after the resolution of the TMD is important, since the persistence of even a small clone of trisomic cells presumably carries risk for subsequent complications of DS, in particular the increased risk of subsequent leukemia.[15] The observation, in our first patient, of a duplicated systemic chromosome 21 in the trisomic clone suggests the possibility of a de novo clonal transformation with the hematopoietic compartment as the initiating event in TMD, much as clonal chromosomal transformations may initiate leukemic changes in older persons.[11] We reasoned that if trisomic cells persisted after resolution of TMD, some would be found within the myeloid cell line. The use of demecolcine-arrested, GM-CSF–stimulated, cultured bone marrow mononuclear cells provided ample metaphases for the cytogenetic evaluation of the myeloid progenitor cells. We found no trisomic cells among 50 metaphases from the marrow of our second patient at 18 weeks of age. This provides strong evidence favoring the complete disappearance of the trisomic clone. It remains possible that trisomic cells are still present in some other cell line, in extremely small numbers among the myeloid progenitor cells, or in a noncycling progenitor cell population that is unresponsive to GM-CSF.

The reports of TMD occurring in infants without stigmata of DS and the strong association of trisomy 21 with spontaneous remission suggest that all phenotypically normal infants with congenital leukemia should be examined for the possibility of trisomy 21 mosaicism. In patients where trisomy is discovered in the apparent leukemic cells, the patients should be treated as patients with DS. Children who undergo spontaneous resolution of leukemia (TMD) should have serial cytogenetic evaluation of blood and marrow cells and cytogenetic evaluation of nonhematopoietic tissue to determine the extent of the trisomic clone. When necessary, cytogenetic evaluation of myeloid progenitor cells can be carried out to determine if the abnormal clone has persisted or resolved.

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Atrioventricular Canal in Down Syndrome

Prevalence of Associated Cardiac Malformations Compared With Patients Without Down Syndrome

Bruno Marino, MD; Ugo Vairo, MD; Antonio Corno, MD; Simonetta Nava, MD;
Paolo Guccione, MD; Raffaele Calabrò, MD; Carlo Marcelletti, MD

• The atrioventricular canal is the "classic" congenital heart anomaly in Down syndrome. We may learn more of the nature of this disorder by careful study of the anatomic characteristics of the cardiac lesions and by comparing these lesions in patients with and patients without Down syndrome. We reviewed the clinical characteristics (echocardiographic and angiocardiographic) of 220 patients with atrioventricular canal and compared the prevalence of anatomic types and associated cardiac malformations in children with (105) and without (115) Down syndrome. In patients with Down syndrome, the complete form of atrioventricular canal was prevalent, with a high frequency of associated Fallot's tetralogy. Partial atrioventricular canal and left-sided anomalies were more common in patients without Down syndrome. Down syndrome is associated with a simpler type of atrioventricular canal when compared with patients with a normal chromosome configuration.

(*AJDC.* 1990;144:1120-1122)

The atrioventricular canal (AVC) is a common congenital heart malformation in patients with Down syndrome (DS).[1] This cardiac malformation, either isolated or associated with other congenital heart disease, occurs also in patients without DS.[2,3] A large number of clinical,[4,5] anatomic,[2,3,6-15] and surgical reports[16-18] have described the cardiac malformations associated with the AVC, but few investigators have correlated the types of these associated anomalies with the presence of DS[2-5]; we could not discern a complete profile of AVC in patients with DS from a review of published reports. Therefore, we investigated the differences between patients with and without DS who had AVC. We attempted to classify the structure of the major cardiac malformation and of the associated anomalies. We had previously reported similar discrimination for ventricular septal defect.[19] The surgical results for repair of AVC defects has been similarly analyzed.[20]

SUBJECTS AND METHODS

The clinical records, two-dimensional echocardiographic studies, and cardiac catheterization and angiocardiographic results for 220 patients with AVC were reviewed. Only patients with situs solitus of the atria were considered; patients with atrial isomerism (splenic syndrome) were excluded, and situs inversus was not found in our series. All patients had chromosomal analysis performed. The definitive cardiac diagnosis was established by a combination of two-dimensional echocardiographic and angiocardiographic data using the same method and by the same interpreters (B.M. and U.V.). The diagnoses were confirmed by surgical inspection or by autopsy in 208 cases. The basic structure of AVC was classified in two types: partial AVC (ie, ostium primum atrial septal defect with cleft of the anterior leaflet of the mitral valve) and complete AVC (ie, ostium primum atrial septal defect confluent with an inlet ventricular septal defect with common atrioventricular valve).[3-8,11] To categorize the associated cardiac anomalies, we analyzed (1) systemic and pulmonary venous connections and atrial structure; (2) the atrioventricular valves and the ventricular septum; (3) ventricular dominance; (4) systemic and pulmonary outflow tracts and the great arteries; and (5) the conotruncal structure. The type of AVC (partial or complete) and the associated cardiac anomalies were compared between the two groups (with or without DS). The retrospective analysis of the cardiac studies and the classification of the AVC types and of the associated anomalies were performed without knowing the karyotype of the patients. Statistical analysis was performed by χ^2 test, and significance was accepted at $P<.05$.

RESULTS

Among 220 patients, there were 105 (47.7%) with DS (group 1) and 115 (52.3%) without DS (group 2). In group 2, we found two patients with Ellis-van Creveld syndrome, one patient with trisomy 9,[21] one patient with partial deletion of chromosome 8, one patient with DiGeorge syndrome, and 35 patients with minor phenotypic anomalies.[22,23]

Types of AVC

Among the 220 patients with AVC, 130 (59%) showed a complete form (80 [61.5%] with DS and 50 [38.5%] without DS) and 90 patients (41%) a partial form (25 [28%] with DS and 65 [72%] without DS; Table). The DS was most commonly associated with a complete AVC ($P<.01$), and the patients without DS most commonly had a partial form of AVC.

Associated Cardiac Malformations

Among the 220 patients, 112 (50.9%) had a total of 137 associated malformations. The associated cardiac anomalies are significantly more frequent ($P<.0001$) in patients without DS (87 vs 47 in patients with DS).

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From the Department of Pediatric Cardiology and Cardiac Surgery, Bambino Gesu' Hospital and Research Institute, Rome (Drs Marino, Vairo, Corno, Nava, Guccione, and Marcelletti); and the Department of Pediatric Cardiology, Monaldi Hospital, Naples (Dr Calabrò), Italy. Dr Corno is now with San Raffaele Hospital, Milan, Italy.

Reprint requests to Dipartimento Medico-Chirurgico di Cardiologia Pediatrica, Ospedale Bambino Gesu', Piazza Sant'Onofrio, 4 00165 Rome, Italy (Dr Marino).

Types of AVC and Associated Cardiac Anomalies in 220 Cases*

Associated Cardiac Anomalies	Partial	Complete	DS	No DS	Total
L superior vena cava	7	8	7	8	**15**
Double outlet R atrium	3	0	0	3	**3**
Double mitral orifice	4	0	0	4	**4**
"Parachute" mitral valve	8	2	2	8	**10**
Additional ventricular septal defect	2	7	1	8	**9**
Hypoplastic ventricle					
L	8	10	5	13†	**18**
R	0	1	1	0	**1**
Subaortic stenosis	6	7	4	9	**13**
Aortic coarctation	12	13	5	20†	**25**
Patent ductus arteriosus	5	7	6	6	**12**
Peripheral pulmonary stenosis	0	1	0	1‡	**1**
Fallot's tetralogy	0	19§	14‖	5	**19**
Double outlet R ventricle	0	3	2	1	**3**
Corrected transposition of great arteries	0	1	0	1	**1**

*AVC indicates atrioventricular canal; DS, Down syndrome.
†$P<.01$.
‡This patient had DiGeorge syndrome.
§$P<.0001$.
‖$P<.05$.

Systemic and Pulmonary Venous Connections and Atrial Structure

The inferior and the right superior vena cava were normally connected with the right atrium in all patients. A persistent left superior vena cava was present in 15 patients, eight with and seven without DS; it was connected with the coronary sinus in 11 cases and with the left atrium in four. Furthermore, three patients with partial AVC without DS showed a significant left displacement of the atrial septum (so-called double outlet right atrium). The pulmonary veins were normally connected with the left atrium in all patients.

Atrioventricular Valves and Ventricular Septum

We recognized a double mitral orifice in four patients (1.8%), all with a partial form of AVC and without DS. A "parachute" mitral valve (single papillary muscle of the left ventricle) was diagnosed in 10 patients (4.5%), eight with partial (all without DS) and two with complete (both with DS) AVC. An additional muscular ventricular septal defect was present in nine patients (4.1%; only one with DS), seven with complete and two with partial AVC. All but one patient had concordant atrioventricular connection.

Ventricular Dominance

While 201 cases had a balanced form of AVC, 18 patients (8.2%), five of them with DS, showed a right ventricular dominance with hypoplastic left ventricle; 10 of these had a complete and eight a partial form of AVC. One patient (0.4%) with DS and complete AVC showed a left ventricular dominance.

Systemic and Pulmonary Outflow Tracts and Great Arteries

Subaortic stenosis was present in 13 patients (5.9%), seven with the complete and six with the partial form of AVC. Four patients with this associated malformation had DS. An aortic coarctation was found in 25 patients (11.4%), 13 with complete and 12 with partial AVC. The patients without DS (20 vs 5) were prevalent ($P<.01$) in this group. Five patients (2.3%), three with complete and two with partial AVC (only one with DS), had a pulmonary valvular stenosis. Patent ductus arteriosus was recognized in 19 patients, 11 with complete and eight with partial AVC; 12 had DS and seven did not. One patient (0.4%) had complete AVC without DS and DiGeorge syndrome with peripheral stenosis of the pulmonary arteries.

Conotruncal Malformations

Fallot's tetralogy was diagnosed in 19 patients (8.6%), all with complete AVC ($P<.001$), 14 of these with DS ($P<.05$). Double outlet right ventricle occurred in three patients with complete AVC, two of these with DS. One patient (0.4%) with complete AVC and without DS presented ventricular inversion with corrected transposition of the great arteries. Transposition of great arteries and truncus arteriosus were not found.

COMMENT

We found two previous anatomic studies on the AVC[2,3] that correlated the presence of DS with associated cardiac anomalies, and two clinical studies that analyzed only left-sided obstructions.[4,5] Because the prevalence of congenital heart disease may be different in autopsy and clinical series,[2-15,24] we studied a large population of children with AVC, to confirm, in clinical practice, the difference between patients affected by AVC with or without DS.

The complete AVC is more common in patients with DS ($P<.01$), and in general the associated cardiac malformations are more common in patients without DS ($P<.0001$). In particular, children with DS and partial AVC (Table) seem not to have any kind of associated cardiac anomalies; in patients with DS and complete AVC, the only prevalent associated malformation we found was Fallot's tetralogy ($P<.0001$; Table). In patients without DS, the hypoplastic left ventricle and the aortic coarctation are more common ($P<.01$), while the additional ventricular septal defect is more common only in complete AVC ($P<.05$). In children without DS, all the anomalies of the left side of the heart are more common, but not significantly so: leftward displacement of the atrial septum ($P=.28$), double mitral orifice ($P=.15$), parachute mitral valve ($P=.14$), and subaortic stenosis ($P=.33$) were all analyzed.

It is well known that patients with DS present certain congenital heart malformations and seem to be "protected" from other cardiac anomalies.[1-18] Different genetic situations may result in different congenital forms of heart disease. In accordance with previous anatomic studies[2,3] and based on our clinical data, children with DS and AVC have predictable associated cardiac anomalies that differ from those occurring in patients with AVC and without DS.

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In Other AMA Journals

JAMA

Blood Pressure, Fitness, and Fatness in 5- and 6-Year-Old Children
B. Gutin; C. Basch; S. Shea; I. Contento; M. DeLozier; J. Rips; M. Irigoyen; P. Zybert (*JAMA.* 1990;264:1123)

Preconception Care
B. W. Jack; L. Culpepper (*JAMA.* 1990;264:1147)

Effect of Inhaling Heated Vapor on Symptoms of the Common Cold
M. L. Macknin; S. Mathew; S. V. Medendorp (*JAMA.* 1990;264:989)

Prevalence of Reading Disability in Boys and Girls
S. E. Shaywitz; B. A. Shaywitz; J. M. Fletcher; M. D. Escobar (*JAMA.* 1990;264:998)

Sports Medicine

William B. Strong, MD, Augusta, Ga
Carl L. Stanitska, MD, Pittsburgh, Pa
Ronald E. Smith, PhD, Seattle, Wash
Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*The authors, in this article, have brought to the attention of pediatricians an awareness of the dichotomy between physical activity patterns and two components of health-related physical fitness (ie, aerobic power and body composition). They also raise the issue of the means by which physical activity is frequently measured (ie, parent/teacher reports or diaries). As we become more conscious of our role as proponents for health promotion and disease prevention activities, this article will provide an understanding of the relationship between physical activity and physical fitness. This study also demonstrates the multiplicity of determinants of physical fitness of children and the need for additional research. Recent data strongly support the observation that increased levels of physical fitness are associated with a reduced incidence of coronary artery mortality.*—W.B.S.

Associations Between Physical Activity and Physical Fitness in American Children

Russell R. Pate, PhD; Marsha Dowda, MSPH; James G. Ross, MS

• Associations between two measures of physical fitness, 1.6-km run/walk performance and sum of three skinfold thicknesses, and selected physical activity factors were studied in a nationally representative sample of third- and fourth-grade students (1150 boys, 1202 girls). Twenty physical activity variables measured via parent and teacher questionnaires were factor analyzed, and for each of the resultant eight factors, individual factor scores were generated. These were used in two multiple regression analyses in which 1.6-km run/walk time and sum of skinfold measurements were the dependent variables. Multiple R^2 for these two analyses were .21 and .18. Significant factors in both analyses were global ratings of the child's activity level, age, vigorous community activities, and gender. The results indicate that physical activity and physical fitness are significantly, although moderately, associated in young children and suggest that interventions directed toward enhancement of physical activity in children are worthy of investigation.

(*AJDC.* 1990;144:1123-1129)

The health benefits of regular physical activity during adulthood have been extensively documented.[1-3] However, much less is known about the short- and long-term health effects of exercise in children.[4,5] Nevertheless, exercise habits and physical fitness in children have long been a stated concern of educators[6,7] and more recently these issues have received the attention of physicians and public health professionals.[5,8-11] Indeed, the 1990 health objectives for the nation include three objectives that pertain directly to physical fitness and exercise in children.[12]

Youth fitness authorities have contended, for more than three decades, that a large percentage of American youngsters are less physically fit than desirable.[13,14] The exact percentage of children who are unfit is controversial, because different fitness testing programs have adopted different criterion-referenced standards.[15,16] However, virtually all the programs find that 20% or more of youngsters fail to meet recommended standards in one or more ar-

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From the School of Public Health, University of South Carolina, Columbia (Dr Pate and Ms Dowda); and Macro Systems, Inc, Silver Spring, Md (Mr Ross).

Reprint requests to Department of Exercise Science, School of Public Health, University of South Carolina, Columbia, SC 29208 (Dr Pate).

eas.[17] Frequently, it has been recommended that this problem be attacked via measures such as expanded physical education (PE) programs in the schools and less television watching at home.[18-21] While these recommendations may be logical, they are based on very scant scientific evidence. Despite the long-standing focus on the youth fitness issue, very few scientific studies have been directed toward identification of the causes of low physical fitness in children. Several experimental studies using small groups have found children to be physiologically responsive to intense exercise training.[22-24] Larger-scale activity interventions in schools have yielded inconsistent results.[21] A review of the epidemiologic literature reveals no previous large-scale, population-based study of behavioral and environmental factors that might be related to physical fitness in young children. A knowledge of these factors, as observed in free-living youngsters, could conceivably provide valuable guidance for the design of public health efforts directed toward enhancement of physical fitness in such youngsters. An important first step is to determine whether physical activity factors are significantly associated with physical fitness in the population of young children.

The present study was designed to examine the associations between measures of participation in physical activity and health-related physical fitness in children. Specifically, in a nationally representative sample of 8- to 9-year-old children, we examined the associations between measures of selected factors related to physical activity habits, as reported by parents and teachers, and two common field tests of fitness, time for the 1.6-km run/walk and sum of three skinfold thickness measurements. Skinfold thickness was taken as a measure of fitness because body composition is now generally accepted as a component of health-related physical fitness[25] and is largely independent of other fitness measures.[26]

SUBJECTS AND METHODS

Subjects for this study were drawn from the sample of third- and fourth- grade students who participated in the National Children and Youth Fitness Study II (NCYFS II). The NCYFS II sample was produced by carving the 50 states of the United States and

Table 1.—Descriptive Data for Total NCYFS II* Sample of Third- and Fourth-Grade Students and for the Subsample of Students Whose Data Were Included in All Statistical Analyses

	Male Subjects		Female Subjects	
Variable	**Mean**	**SD**	**Mean**	**SD**
Total Sample: N = 1150 for Males; N = 1202, Females				
Age, y	8.74	0.75	8.63	0.71
Height, cm	136	6.8	135	7.3
Weight, kg	32.8	7.8	32.5	8.1
1.6-km run/walk, min	10.66	2.39	11.65	2.49
Sum of three skinfolds, mm	31.07	16.98	37.82	17.95
Subsample: N = 776 for Males; N = 782, Females				
Age, y	8.78	0.70	8.66	0.66
Height, cm	136	6.6	135	7.3
Weight, kg	32.5	7.5	32.2	8.3
1.6-km run/walk, min	10.55	2.12	11.59	2.15
Sum of three skinfolds, mm	30.47	16.40	37.78	17.44

*NCYFS II indicates National Children and Youth Fitness Study II.

Table 2.—Physical Activity Variables and Zero-Order Correlations of Each With Log 1.6-km Run/Walk Time and Log Sum of Skinfold Thicknesses (N = 2352)

	Log 1.6-km Run/Walk		Log Sum of 3 Skinfolds	
Physical Activity Variable*	**Correlation Coefficient**	***P* Value**	**Correlation Coefficient**	***P* Value**
Physical education (PE) and other school variables				
A. Percentage of classes taught by PE specialist	−.13	<.01	+.01	.57
B. Minutes in PE per week	−.02	.28	+.02	.29
C. Minutes in recess per day	+.04	.06	−.03	.16
D. Percentage of PE class time spent in vigorous activity	+.03	.24	−.01	.58
E. Minutes of PE class spent in administrative matters	−.06	.01	+.02	.47
F. Minutes of activity in average PE class	−.03	.21	+.03	.25
G. Usually take PE on school grounds (yes, no)	+.10	<.01	+.03	.10
H. Warm climate (yes, no)	+.14	<.01	+.04	.04
Child's participation in community-based physical activities				
I. Public park or recreation department (yes, no)	−.03	.25	−.03	.23
J. Church (yes, no)	+.01	.58	−.01	.58
K. Sports team or league (yes, no)	−.22	<.01	−.10	<.01
L. YMCA, YWCA, or similar organization (yes, no)	−.05	.03	−.08	<.01
M. Health club, spa, or private lesson (yes, no)	−.10	<.01	−.03	.16
N. Brownies, Cub Scouts, or other scouting group (yes, no)	−.05	.02	<.01	.99
O. 4-H or other farm club (yes, no)	−.03	.12	<.01	.89
P. Sum of community activities (seven items above)	−.17	<.01	−.08	<.01

(cont)

the District of Columbia into two tiers: an urban tier, consisting of 12 regional strata constituting the 60 largest standard metropolitan statistical areas, as defined by the US census, and a nonurban tier, consisting of 13 regional strata constituting all counties outside the 60 largest standard metropolitan statistical areas. From each of the 25 regions, which were of approximately equal size, one primary sampling unit was randomly selected, followed by random subselection of a single county (if the primary sampling unit were a multicounty entity), with probabilities of selection proportional to population size at both steps.

From schools containing the full range of grades of interest in the selected counties, two schools were randomly selected, with the probability of selection again being proportional to the average size of the school enrollment at each grade level. Schools that were too small or did not have the full range of classes were linked with other schools before sampling, so that the grouped schools constituted a single unit and had sufficient students. Finally, from each selected school, at those grades selected for study in the school, one class was selected, with equal probabilities of selection among class sections.

A total of 2352 third- and fourth-grade students (1150 male, 1202 female) participated in NCYFS II and data from this entire sample were included in the first phase of the statistical analyses conducted in this study. Complete sets of data were collected on 1558 third- and fourth-graders (776 male, 782 female) and only the data from this subsample were included in the more advanced statistical analyses. Table 1 provides descriptive data on the total sample and on the subsample. The subsample and the total group were very similar in age, height, weight, and fitness test scores.

Table 2.—Physical Activity Variables and Zero-Order Correlations of Each With Log 1.6-km Run/Walk Time and Log Sum of Skinfold Thicknesses (N=2352) (cont)

	Log 1.6-km Run/Walk		Log Sum of 3 Skinfolds	
Physical Activity Variable*	**Correlation Coefficient**	***P* Value**	**Correlation Coefficient**	***P* Value**
Child's participation in community-based physical activities (cont)				
Q. Number of community-based activities that were organized	−.17	<.01	−.14	<.01
R. Number of community-based activities that were vigorous	−.07	<.01	−.05	.01
Global rating of child's activity level				
S. Teacher's rating (>1 to <5)	+.24	<.01	+.33	<.01
T. Parent's rating (>1 to <5)	+.17	<.01	+.29	<.01
Television watching				
U. Hours per day child watches television (parent's estimated)	+.09	<.01	+.09	<.01
Parental activity habits				
V. Mother's exercise (days in typical week)	−.04	.10	−.08	<.01
W. Father's exercise (days in typical week)	<.01	.97	−.06	<.01
X. Mother exercises with child (days in typical week)	−.02	.46	−.04	.05
Y. Father exercises with child (days in typical week)	−.05	.02	−.06	<.01
Z. One or both parents exercise with child (days in typical week)	−.02	.36	−.06	.01
AA. Mother's physical activity level (>1 to <5)	+.05	.02	+.07	<.01
BB. Father's physical activity level (>1 to <5)	+.02	.39	+.03	.14

*Yes=1; No=0; YMCA, Young Men's Christian Association; and YWCA, Young Women's Christian Association.

Variables Related to Physical Activity

Two questionnaires were used in collecting information about each subject's physical activity habits. One survey instrument was completed by the subjects' teachers and provided information concerning the school PE program in which the subjects participated. The variables assessed are listed in Table 2 (variables A through H). Also, the teacher provided a global rating of each child's physical activity level (Table 2, variable S).

A second questionnaire was completed by the subject's parent or guardian. Included in this instrument were questions concerning the child's participation in physical activities in various community-based settings (Table 2, variables I through R). Parents also reported the hours per day spent by the child in television watching and they provided a global rating of the child's physical activity level. In addition, this instrument was used to collect information about the physical activity habits of the parents (Table 2, variables V through BB). Neither of the questionnaires used in this study had been tested for reliability.

Physical Fitness Measures

A primary goal of NCYFS II was the establishment of national norms for health-related physical fitness in 6- to 9-year-old children. Participating children completed a five-item test battery that included measures of low back/hamstring flexibility, abdominal muscle strength/endurance, and upper body muscular strength/endurance, as well as body composition and cardiorespiratory endurance. Only the data for the measures of the latter two physical fitness components were used in the present investigation.

Participating students were oriented to the testing procedures by their PE teachers well in advance of the scheduled test date. All physical fitness test data were collected by trained specialists who moved from site to site within a designated geographic area. These specialists, of whom there were five, were trained by two of the principal investigators (R.R.P. and J.G.R.) and were monitored by on-site visits and telephone contact to ensure proper quality control.[27] Interobserver reliability coefficients were determined in the field for the skinfold item and the mean for these was 0.99.[27]

Body composition was assessed by measuring skinfold thicknesses at the triceps, subscapular, and medial calf sites.[27] Skinfold (Lange) calipers, calibrated daily, were employed and each measure was taken at least three times until three consecutive measures within 2 mm were obtained. The sum of the three skinfold thickness measures was used in the analyses conducted in this study. Such measures recently have been reported to correlate highly with percentage of body fat in children.[28]

In the third- and fourth-graders, cardiorespiratory endurance was measured using a 1.6-km run/walk for time test. This is a common field test of cardiorespiratory endurance and it is included in several current physical fitness test batteries.[15,16] Concurrent validity of distance run tests with directly measured maximal aerobic power (VO_2max) has been previously established.[29] Among 8- to 10-year-old subjects, validity coefficients for the 1.6-km run/walk in the range of 0.6 to 0.7 have been observed.[30] For administration of the 1.6-km run/walk tests, children were organized into small groups (N=6 to 10) that ran on level, measured circuits ranging in length from 0.2 to 0.4 km.

Statistical Analyses

All statistical analyses were conducted using computer programs available in the SAS package.[31] Initially, using data for the entire NCYFS II sample of third- and fourth-graders (N=2352), Pearson correlation coefficients were computed between each of the 28 variables and the log of two fitness measures. Log transformations were performed since the two fitness variables had been found to be positively skewed. Each physical activity variable that was found to be significantly correlated ($P \leq .05$) with either of the fitness measures was included in subsequent analyses. Next, a principal component factor analysis was conducted on this set of physical activity variables employing the data of subjects on whom complete data sets were available. The eight factors that resulted from this analysis were rotated using the varimax procedure.

For each of the eight factors, factor score coefficients were computed for each subject using the SCORE program of SAS. These coefficients were used as the independent variables in two multiple regression analyses. In one of these analyses, log-adjusted 1.6-km run/walk time was the dependent variable; in the other, the dependent variable was the log-adjusted sum of three skinfold thickness measurements. In both of these regression analyses, age and gender were also entered as independent variables. These analyses were conducted using a stepwise multiple regression procedure in which all variables in the model were evaluated for significance at each step. Only variables contributing significantly to a model were included. An analysis was discontinued when none of the remaining variables produced a significant F statistic when added to the model.

The weight option was used in the analysis so that the results would be reflective of the national population of third- and fourth-grade students. A case-weight variable was available for each child. The case-weight mean was obtained for each grade-gender group. The case-weight value for each child was normalized by dividing by the appropriate mean. This normalized case weight was the variable used in the weight statement.

Table 3.—Rotated and Standardized Factor Patterns for Physical Activity Variables (a Cut-off Value of 0.30 Was Used for the Factor Loadings)

Factor	Physical Activity Variables Include*	Standardized Scoring Coefficient	Interpretative Label
1	X	.61	Parental exercise with child
	Y	.62	
2	K	.31	Vigorous community activities
	Q	.37	
	R	.42	
3	G	.52	Physical education on school grounds
	H	.53	
4	V	−.50	Mother's exercise
	AA	.60	
5	M	.63	Private club or lesson; television watching
	U	−.45	
6	S	.58	Global ratings of child's activity level
	T	.52	
7	N	.32	Scouts; father's exercise
	W	.65	
8	A	.49	Physical education specialist; Y activity†
	E	.54	
	L	−.51	

*Variables are defined in Table 2.

†Y indicates Young Men's Christian Association, Young Women's Christian Association, or similar organization.

Table 4.—Summary of Stepwise Multiple Regression Analysis of Relationship Between Log of the Sum of Three Skinfolds and Physical Activity Factors, Age, and Gender

Step	Variable	Regression Coefficient	*P* Value	Model F	*P* Value	R^2
1	Intercept	3.43				
	Factor 6	0.16	.0001	257.18	.0001	.1418
2	Intercept	3.20				
	Gender	0.15	.0001	158.76	.0001	.1696
	Factor 6	0.15	.0001			
3	Intercept	2.85				
	Gender	0.16	.0001	108.68	.0001	.1734
	Age	0.04	.0072			
	Factor 6	0.15	.0001			
4	Intercept	2.85				
	Gender	0.16	.0001	83.48	.0001	.1770
	Age	0.04	.0086			
	Factor 4	0.03	.0098			
	Factor 6	0.14	.0001			
5	Intercept	2.87				
	Gender	0.15	.0001	67.83	.0001	.1793
	Age	0.04	.0094			
	Factor 2	−0.02	.0346			
	Factor 4	0.03	.0102			
	Factor 6	0.15	.0001			

RESULTS

As indicated by the data presented in Table 2, 20 of the 28 physical activity variables were found to correlate significantly with either 1.6-km run/walk time or sum of the three skinfold thickness measurements ($P \leq .05$). Approximately one half of these correlation coefficients, although significant, were quite low in absolute magnitude ($r < .10$). The remaining variables were moderately associated with the fitness measures ($r=.10$ to .33). Sixteen variables correlated with 1.6-km run, 15 variables correlated with skinfold thickness, and 11 variables correlated with both of the fitness measures. In general, the PE and school variables tended to correlate significantly with the 1.6-km run time but not with skinfold thickness. Community activity variables, global ratings of the child's activity level, and television watching tended to correlate significantly with both fitness tests. Parental activity variables tended to be significantly associated with the child's skinfold thickness but they were somewhat less likely to be associated strongly with 1.6-km run/walk time. We consider it noteworthy that the global ratings of the child's activity level, as reported by both parents and teachers, were significantly correlated with both fitness measures ($r=.17$ to .33).

Factor analysis of the 20 variables that correlated significantly with at least one of the fitness measures yielded eight factors. The results of this factor analysis are summarized in Table 3. Most of the factors could be readily interpreted and Table 3 includes our interpretive label for each factor.

The results of the multiple regression analysis in which the sum of skinfold thickness measurements was entered as the dependent variable are summarized in Table 4. A total of five independent variables entered the resultant multiple regression model and R^2 for the complete model was .1793. Variables entering the model were gender, age, and factors that had been labeled "vigorous community activities," "mother's exercise," and "global ratings of the child's activity."

Table 5.—Summary of Stepwise Multiple Regression Analysis of Relationship Between Log of Kilometer Run/Walk Time and Physical Activity Factors, Age, and Gender

Step	Variable	Regression Coefficient	*P* Value	Model F	*P* Value	R^2
1	Intercept	2.38				
	Factor 6	0.06	.0001	188.14	.0001	.1079
2	Intercept	2.38				
	Factor 2	−0.04	.0001	136.65	.0001	.1495
	Factor 6	0.06	.0001			
3	Intercept	2.68				
	Age	−0.03	.0001	102.93	.0001	.1658
	Factor 2	−0.04	.0001			
	Factor 6	0.06	.0001			
4	Intercept	2.72				
	Age	−0.04	.0001	85.94	.0001	.1812
	Factor 2	−0.04	.0001			
	Factor 5	−0.02	.0001			
	Factor 6	0.06	.0001			
5	Intercept	2.63				
	Gender	0.05	.0001	75.24	.0001	.1951
	Age	−0.04	.0001			
	Factor 2	−0.03	.0001			
	Factor 5	−0.02	.0001			
	Factor 6	0.06	.0001			
6	Intercept	2.65				
	Gender	0.05	.0001	67.33	.0001	.2066
	Age	−0.04	.0001			
	Factor 2	−0.03	.0001			
	Factor 3	0.02	.0001			
	Factor 5	−0.03	.0001			
	Factor 6	0.06	.0001			

The multiple regression analysis of the relationships between 1.6-km run/walk time and age, gender, and the physical activity factors is summarized in Table 5. A six-variable model resulted from the analysis and the full model accounted for approximately 21% of the variance in 1.6-km run/walk performance ($R^2=.2066$). As was the case for the multiple regression analysis of the sum of skinfold thickness measurements, factor 6 (global ratings of the child's activity level) was the first variable entering the model. Also accounting for significant variance in 1.6-km run/walk performance were gender, age, and factors labeled "vigorous community activities," "PE on school grounds" and "television watching; private lesson or club."

COMMENT

The results of this study demonstrate that physical activity and physical fitness are significantly associated in 8- to 9-year-old children. In general, the zero-order correlation coefficients between the measures of physical activity and the two observed fitness measures were low in absolute magnitude. However, it should be noted that virtually all of the statistically significant zero-order correlations were in the direction that would be hypothesized on the basis of the documented effects of exercise. That is, higher levels of physical activity were associated with better status on the fitness measures. A strength of the present study is that it employed a nationally representative sample of third- and fourth-grade students. As such, the observed associations should reflect relationships that exist in the population of contemporary American 8- to 9-year-old children.

The conclusion that activity and fitness are significantly associated is supported by the results of the multiple regression analyses. These analyses demonstrated that 18% to 21% of the variance in fitness status could be accounted for by the physical activity factors that were formed via factor analysis of the observed physical activity variables ($R^2=.18$, .21). The finding that approximately one fifth of the variance in fitness status was accounted for by the activity measures is particularly impressive when considered in the light of previously published research from related fields. First, it is widely accepted that fitness and physical activity are associated in adults, but it is often overlooked that the strength of this association is modest at best. For example, Sobolski and colleagues[32] reported correlation coefficients of .10 and .07 for the associations between leisure-time physical activity and physical working capacity and between occupational physical activity and physical working capacity, respectively. Other studies have reported somewhat stronger associations between physical activity and physical fitness, but the reported correlation coefficients have not exceeded .5.[33-35] Second, the work of Bouchard and Malina[36] suggests that 40% to 50% of variance in maximal aerobic power (Vo_2max) is accounted for by genetic factors. Studies of twins and adoptive families indicate that heritability of body fatness is at least this great and probably greater.[37,38] Therefore, it might be assumed that, at most, 50% to 60% of the variance in fitness test performance remains to be accounted for by all environmental and behavioral factors. For the two fitness tests examined in this study, these factors would include dietary habits (for the skinfold tests) and test familiarity and motivation (for the 1.6-km run) as well as habitual physical activity. Examined against this background, the findings of the present study provide support for the contention that higher levels of habitual physical activity are associated with higher levels of physical fitness, even in young children. However, our data also show that much of the variability in fitness in children is not accounted for by the activity-related factors examined in this study. Clearly, the body of knowledge concerning the determinants of physical fitness in children is incomplete, and additional studies employing more burdensome measures of activity history and other environmental factors are needed.

Over the past three decades several large-scale national studies of physical fitness in American children have been conducted.[14] Most of these studies have focused only on physical fitness and have failed to measure physical activity. However, some of the more recent large-scale studies have attempted to measure both activity patterns and fitness.[39,40] This approach appears appropriate because available evidence suggests that long-term health outcomes are associated, perhaps independently, with both activity and fitness.[41] The results of the present study support the efficacy of assessing physical activity in large populations of children. As noted above, the associations between the activity variables and the fitness measures, although low in absolute magnitude, were significant and in the expected direction. The significant association between physical activity and 1.6-km run/walk performance is notable because of the acknowledged difficulty involved in assessing activity in youngsters[42] and because children, as compared with adults, are relatively homogeneous in terms of fitness. The best individual predictors of fitness were the global activity ratings provided independently by parents and teachers. It should be noted that, in the factor analysis performed in this study, both of these variables loaded on the same factor (factor 6). This factor was the first selected for entry in both of the multiple regression analyses performed and was found to be quite robust in that it was significantly associated with the dependent variable (fitness measure) in each step of both multiple regression analyses. This observation is consistent with the previous report of Murphy et al[43] and indicates that meaningful information about the physical activity habits of young children can be obtained simply by asking parents and teachers to rate the child's activity relative to that of his or her peers.

The results of the multiple regression analyses provide important information regarding the activity factors that are most strongly and independently associated with fitness in young children. As noted above, the single factor accounting for the greatest variance in both 1.6-km run/walk time and sum of skinfold thickness measurements was the one labeled global ratings of child's activity level. The only other factors to enter both regression analyses were gender, age, and vigorous community activities.

Aside from age, gender, and the global activity ratings and vigorous community activity factors, different sets of factors entered the multivariate models for the two fitness measures. With the sum of skinfold thickness measurements, mother's exercise entered the model, whereas with 1.6-km run/walk, PE on school grounds and private club/television watching accounted for significant fractions of variance. The meaning of these associations cannot be interpreted with great confidence. However, these results may indicate that 1.6-km run/walk performance is most strongly associated with involvement in relatively intense exercise, exposure to which is more frequent in better PE programs and in structured community-based activity programs. The finding that television watching time was negatively associated with 1.6-km run/walk performance is consistent with the claims of fitness authorities and with the findings of other recently reported studies.[20,44] In contrast, body composition may be importantly affected by the home environment as represented by the mother's activity behavior. The linkage between parental activity and fitness in children is consistent with the findings of Sallis et al[45] who found a significant association between parental vigorous activity and child physical activity. Therefore, it may be that more active parents encourage, either directly or as role models, higher levels of activity in their children who, consequently, manifest higher levels of fitness. This hypothesis seems worthy of further study.

Our finding that physical activity and physical fitness are significantly associated in young children may provide important guidance for public health officials and educators. The data presented indicate that more physically active children are more physically fit and imply that broad-scale exercise intervention programs should result in improvements in youth fitness. This implication is supported by the results of controlled training studies that have documented the "trainability" of children[22-24] and by the outcomes of a few large-scale trials in which school PE programs have been modified to provide more activity.[46-49] However, it must be emphasized that the associations noted in the present study are based strictly on cross-sectional observations. As such, we are reluctant to infer the presence of a cause-effect relationship between physical activity and physical fitness. It is, of course, possible that less fit children tend to opt for a less active life-style. Nevertheless, at the very least, the results of this study indicate that the effects of physical activity intervention programs on the physical fitness of children should be further evaluated using large-scale, longitudinal study designs.

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Pertussis in Hospitalized Children

Vanthaya N. Gan, MD, Trudy V. Murphy, MD

• Before the whole-cell pertussis vaccine was available, *Bordetella pertussis* infections were an important cause of morbidity and mortality in infants. To determine the extent of continuing morbidity in an era of vaccination, a retrospective review was conducted of the records of neonates and infants hospitalized with pertussis infection at Parkland Memorial Hospital and Children's Medical Center, Dallas, Tex. During the 20 years from 1967 through 1986,182 patients were younger than 24 months. Among 176 patients whose immunization history was recorded, 89% had received fewer than two doses of pertussis vaccine. The mean hospital stay was 7.4 days (range, 1 to 69 days). A convulsion occurred in 11 patients (6%). Apnea was reported in 45 patients (25%) and observed in the hospital in 26 (14%). Nine patients (5%) received mechanical ventilatory therapy. Intensive care monitoring was required in 18 patients (10%). Three (1.6%) died, all with secondary bacterial pneumonia. This hospital-based population indicates that pertussis continues to be a cause of serious morbidity and mortality in infants.

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Increased publicity describing rare, but serious, reactions after immunization with the whole-cell pertussis vaccine has resulted in decreased acceptance.[1] A decrease in use of pertussis vaccine may have contributed to a 33% increase in cases of pertussis reported to the Centers for Disease Control in 1984 and 1985 compared with cases reported in 1982 and 1983.[2] Fear of reactions following vaccination may not, however, be appropriately balanced by appreciation of the morbidity and mortality resulting from infection, which were clearly defined in the preimmunization era.[3]

Acellular pertussis vaccines are undergoing testing in the United States.[4] More recent information defining the course and complications of pertussis in infants is needed to document the continuing severity of infection and the importance of vaccination. We reviewed the clinical presentation, laboratory findings, course, and complications of pertussis in hospitalized neonates and infants to determine whether these factors have changed during an era when immunization with whole-cell pertussis vaccine has been readily available.[5-11]

PATIENTS AND METHODS

The discharge diagnoses and microbiology laboratory records at Children's Medical Center and Parkland Memorial Hospital, Dallas, Tex, were reviewed to identify patients hospitalized because of pertussis. A case was included in the review if the patient was hospitalized between January 1, 1967, and December 31, 1986; if the patient was younger than 24 months; and if one of the following criteria was met: (1) a positive culture for *Bordetella pertussis* (proved case) or (2) characteristic clinical findings of pertussis and a positive direct fluorescent antibody test of nasopharyngeal secretions for *B pertussis*, or contact with a culture-proved case of pertussis (probable case). Throughout the study period, secretions were obtained from the nasopharynx and inoculated for culture onto either Bordet-Gengou or Regan-Lowe agar medium.[12]

A standard protocol was used to obtain the following information from the medical records: the duration and the characteristics of the cough; history of contact with another case; immunization with pertussis vaccine; the clinical course, including fever (defined as temperature >38°C); and laboratory and radiologic findings. Clinical symptoms, such as paroxysmal cough, character of the cough, and apnea, were recorded as assessed by the medical care provider. It was impossible to verify immunization histories recorded in the medical record. Two proved cases in this series were included in a previous report.[13]

Statistical analysis was performed with χ^2, Fisher's Exact Test, and t tests of independent samples, using two-tailed hypotheses; $P<.05$ was considered significant.

RESULTS

From January 1, 1967, through December 31, 1986, 182 patients hospitalized at Children's Medical Center and Parkland Memorial Hospital satisfied the criteria for review. During the first and second 10-year periods, there were 45 and 137 patients, respectively. Thirty-four (43%) of 80 patients for whom cultures were performed had *B pertussis* isolated from nasopharyngeal secretions (proved cases; Table 1). A fluorescent antibody test was performed on secretions from all patients with proved disease, and 22 (65%) were positive.

There were 148 probable cases. A positive fluorescent antibody test supported the diagnosis in 132 cases. Contact with a proved case of pertussis and clinical findings were the basis of the diagnosis in an additional 16 patients.

Demographic Characteristics

Patients ranged in age from 10 days to 23.1 months (mean, 4.4 months); 169 (93%) patients were younger than 1 year and 13 of these patients (7.1%) were younger than 1 month.

Whole-cell pertussis vaccine had been given to 57 patients (31%; Table 2). More patients had received one or more doses of vaccine during the second compared with the first 10 years (50/137 [36%] vs 7/45 [16%], respectively; $P=.01$).

The racial distribution of cases reflected the population served. Non-Hispanic whites accounted for 51%, Hispanics for 23%, blacks for 26%, and Asians for less than 1%. Fifty-one percent of patients were female.

Pertussis cases were present throughout the year. The cumulative

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From the Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas.

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Table 1.—Diagnostic Studies in 182 Cases of Pertussis by Inclusion Criteria*

Study	Proved (n=34)	Probable (n=148)
Culture for *Bordetella pertussis*	34/34	0/46
Fluorescent antibody test	22/34	132/147

*Values are number positive/number tested.

Table 2.—Age and Immunization Status With Whole-Cell Pertussis Vaccine in 182 Patients*

Age, mo	No. of Doses 0	1	2	≥3	Unknown
<2	77 (42)	16 (9)	2 (1)	...	1 (<1)
3-4	20 (11)	18 (10)	2 (1)	...	2 (1)
5-6	6 (3)	5 (3)	2 (1)	...	0 (0)
7-18	15 (8)	4 (2)	4 (2)	3 (2)	2 (1)
19-23	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)
0-23	**119** (65)	**43** (24)	**10** (5)	**4** (2)	**6** (3)

*Values are number (percent) of patients.

monthly and the annual number of cases are shown in Figs 1 and 2. Almost half of the cases (48.4%) occurred during the late spring and summer months (May through August).

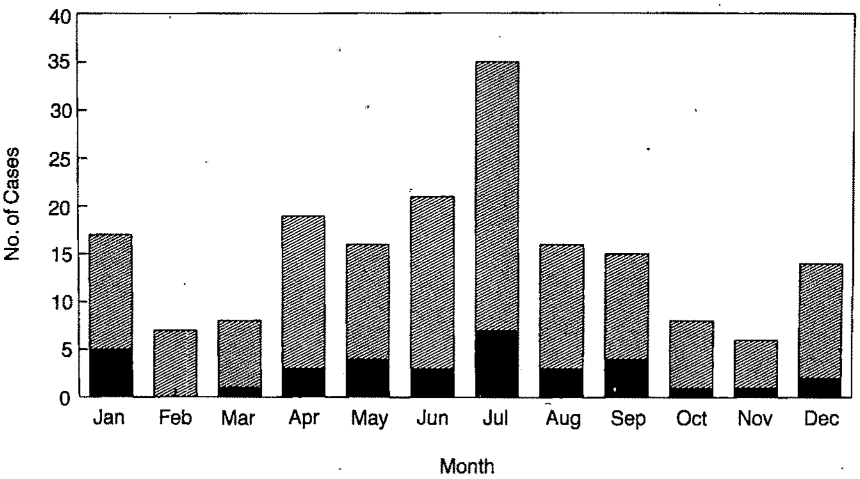

Fig 1.—The cumulative numbers of cases of pertussis are shown by month from 1967 through 1986 in patients younger than 24 months who were hospitalized. Solid portions of bars indicate proved cases; shaded portions, probable cases.

History of Exposure

Exposure to a person with cough was reported for 111 (61%) of 182 patients, of whom 28 (25%) had confirmed pertussis. The ill contact was an adult in 49 cases (44%), a child in 41 (37%), and both adult and child in 21 (19%). The contact was a member of the patient's household or a relative in 105 (95%) of 111 patients. The remaining six patients were exposed at their respective child day-care facility (two patients), to a neighbor (two patients), in an ambulatory medical care clinic (one patient), and at an unknown location (one patient).

Admission Findings

The duration of illness in the catarrhal phase was not recorded. At presentation, all patients had a history of cough. The duration of coughing before admission to the hospital ranged from 1 to 60 days (mean, 11 days; median, 7 days); 62 patients (34%) had a cough for less than a week, and 37 patients (20%) had a cough for more than 2 weeks before admission. Coughing was reported to be paroxysmal in 118 cases (65%; Table 3). The characteristic "whoop" was noted by parents in only 18 patients (10%).

The hemoglobin and hematocrit values ranged from 62 to 204 g/L (mean, 113 g/L) and 0.18 to 0.58 (mean, 0.36), respectively. Total leukocyte counts ranged from 4.4 to 82.4 × 10^9/L (mean, 21.4 × 10^9/L). Total leukocyte counts of 12.7, 18.1, and 25.7 × 10^9/L constituted the 25th, 50th, and 75th quartiles, respectively. Leukemoid reaction (total leukocyte count, >50 × 10^9/L) was present in seven patients (4%).

The proportion of leukocytes that were lymphocytes varied from 0.14 to 0.95 (mean, 0.69). Lymphocyte proportions of 0.60, 0.70, or 0.80 constituted the 25th, 50th, and 75th quartiles, respectively. The absolute lymphocyte counts ranged from 2.0 to 45.2 × 10^9/L (mean, 14.4 × 10^9/L; median, 11.6 × 10^9/L).

A chest roentgenogram was obtained in 157 patients (86%) and was abnormal in 77 patients (49%; Table 4). More than one abnormal finding was present in 19 patients. Perihilar infiltrations were the most frequent abnormality, followed by lobar and diffuse or patchy infiltrates. "Shaggy heart" was described in one patient. Atelectasis was recorded in only 10 patients (6%).

Clinical Course and Outcome

The total hospital stay varied from 1 to 69 days (mean, 7.4 days; median, 5.5 days). The mean and median lengths of hospitalization were longer during the first compared with the second 10 years (9.0 and 7 days vs 6.9 and 5 days, respectively), and fewer patients were readmitted during the first compared with the second 10 years (one [2%] vs six [4%]), but the differences were not statistically significant.

Significantly fewer patients had fever, vomiting, apnea, or cyanosis while hospitalized than did patients reported by parents ($P<.05$; Table 3). By history, patients younger than 3 months compared with older patients had similar rates of apnea (29% vs 20%, respectively). However, in the hospital, patients

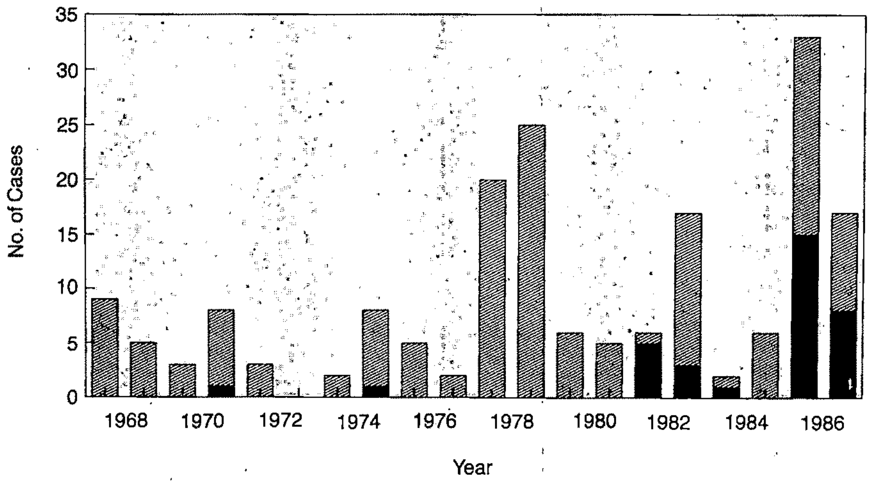

Fig 2.—The annual numbers of cases of pertussis are shown in patients younger than 24 months who were hospitalized for the years 1967 through 1986. Solid portions of bars indicate proved cases; shaded portions, probable cases.

Table 3.—Symptoms and Signs of Pertussis*

Clinical Manifestation	Before Admission	During Hospitalization	P
Paroxysmal cough	118 (65)	117 (64)	NS
Whoop	18 (10)	14 (8)	NS
Fever	61 (34)†	28 (15)	<.001
Vomiting	116 (64)	72 (40)	<.001
Apnea	45 (25)	26 (14)	.02
Cyanosis	108 (59)	79 (43)	.003
Convulsion‡	9 (5)	6 (3)	NS

*Values are number (percent) of patients with manifestation. NS indicates not significant.
†By history.
‡A total of 11 patients (6%) had one or more convulsions.

younger than 3 months had a rate of apnea that was significantly greater than that of older patients (24% vs 3%, respectively; $P<.001$).

The rates of paroxysmal cough, of whooping with coughing, and of convulsion were not significantly different before admission and during hospitalization. However, patients younger than 3 months were more likely to have a convulsion than older patients (10% vs 1%, respectively; $P=.01$). The rates of convulsions did not differ in the first and the second 10 years (three patients [7%] vs eight patients [6%]).

Antibiotics were administered to 177 patients (97%). Erythromycin alone was given to 125 patients (69%). Ampicillin (or amoxicillin) was given to 37 patients (20%), and both ampicillin or erythromycin were given to 15 (8%). The use of erythromycin increased from the first to the second 10 years from 53% to 85% of patients.

Eighteen patients (10%) were admitted to the intensive care unit (ICU). All admissions but one were during the second 10 years. Patients were admitted to the ICU when coughing episodes were associated with severe respiratory distress, apnea, severe bradycardia, or convulsions. Infants less than 3 months of age were more likely than older children to require ICU support (15% vs 5%, respectively; $P=.03$). The average stay in the ICU was 6 days. The majority of cases were managed with conventional means, using increased inspiratory oxygen, mist therapy, and suction. Nine patients (5%) required mechanical ventilation. Parenteral antibiotics were given to 11 patients monitored in the ICU.

Secondary bacterial infection complicated pertussis infection in four patients, one each in 1968, 1983, 1985, and 1986 (Table 5). All had complicating secondary pneumonia either with sepsis or with atelectasis and respiratory failure. None of the infants were immunized against pertussis. Two had received no previous antibiotics, and one each was receiving ampicillin or erythromycin for pertussis when the secondary pneumonia was recognized. Three (1.6%) of the infants died. All were male, all were 1 month of age, and each was the product of a term pregnancy and had previously been healthy. Two had leukemoid reactions at admission, and all had leukemoid reactions before death.

The complications of pertussis were analyzed in relationship to the number of doses of whole-cell pertussis vaccine. Infants who received zero or one dose of vaccine, compared with two doses or with three doses, had a longer mean hospital stay (7.2, 4.6, and 3.8 days, respectively) and higher rates of convulsions (6.1%, 0%, and 0%), apnea (16%, 0%, and 0%), and death (1.8%, 0%, and 0%), but the differences among groups were not statistically significant. Age was an important confounding variable in assessing the effect of vaccine on the rates of complications. The majority of patients (65%) were younger than 4 months of age, and only two (1.7%) of these 118 patients had received more than one dose of whole-cell pertussis vaccine.

COMMENT

This review summarizes features of the illness of 182 patients with pertussis. The specific diagnosis of *B pertussis* infection was supported by a positive culture in 43% (34/80) of those in whom cultures were obtained and by a positive fluorescent antibody test in 85% (154/181) of neonates and infants who had no culture obtained or a negative result.[14] These rates of positive confirmatory tests are consistent with those previously reported.[6,9] Isolation of *B pertussis* is reduced in patients who have received vaccine and with progress of the illness over time.[15] Thirty-one percent of the patients in this review had one or more doses of whole-cell pertussis vaccine, and 45% were already in the second, paroxysmal phase of their illness at presentation. Informa-

Table 4.—Admission Chest Roentgenograms of 157 Patients With Pertussis*

Abnormality	1	>1	Total†
Atelectasis	2	8	**10** (6)
Hyperexpansion	5	3	**8** (5)
"Increased lung markings"	1	1	**2** (1)
Infiltration			
Perihilar	18	8	**26** (17)
Lobar	15	9	**24** (15)
Diffuse or patchy	11	6	**17** (11)
Bronchopneumonia	5	1	**6** (4)
"Shaggy heart"	0	1	**1** (<1)
Cardiomegaly	1	1	**2** (1)

*Twenty-five of 182 patients with pertussis did not have a chest roentgenogram.
†Number (percent) of patients who had roentgenograms. Eighty patients (51%) had chest roentgenograms with no abnormalities. The roentgenograms of 19 showed more than one abnormality.

Table 5.—Clinical Characteristics of Patients With Pertussis With Secondary Bacterial Infection*

	Patient			
Characteristic	1	2	3	4
Age, mo	1	1	1	1
Race/sex	B/M	H/M	B/M	H/M
Illness before admission, d	1	14	7	14
Confirmatory test result				
Culture	−	+	+	+
Fluorescent antibody	+	...	−	...
Admission				
Total white blood cell count, ×10⁹/L	17.8	70.0	54.5	28.0
Lymphocyte proportion	0.55	0.43	0.70	0.68
Hospital stay, d	17	5	4	14
Complications				
Central nervous system	None	Convulsion	None	None
Respiratory				
Pneumonia	RUL	Bronchopneumonia	RLL atelectasis	RUL bronchopneumonia
Other	Cardiopulmonary arrest	...	...	...
Site of culture	Blood	Blood, tracheal aspirate	Lung (postmortem)	Lung (postmortem)
Culture result	*Escherichia coli*	*Pseudomonas aeruginosa*	*Haemophilus influenzae* (nontypable)	*Klebsiella* species
Outcome	Survived	Died	Died	Died

*H indicates Hispanic; RUL, right upper lobe; and RLL, right lower lobe. All patients had paroxysmal cough, apnea, and cyanosis.

tion was not collected regarding the use of antibiotics before cultures for *B pertussis* were obtained. Nevertheless, prior use of antibiotics also could have reduced the rate of positive cultures in our patients.[15]

The premise of this retrospective review was that the morbidity and mortality of pertussis infection have not changed substantially from earlier descriptions, during an era when whole-cell pertussis vaccine has been readily available. Our population was hospital based, and we did not attempt to determine the incidence of pertussis in the community. Undoubtedly, there were other cases of pertussis. In our review alone, we identified an additional 69 patients who were hospitalized with a diagnosis of pertussis. Although the illness in these patients fit clinical diagnoses of pertussis,[16,17] they were excluded because diagnostic studies for pertussis and other agents that mimic pertussis were either negative or not done.[18,19] The findings in these 69 patients were similar to those of proved and probable cases, including two children who died with secondary bacterial complications.

Referral patterns and criteria for admission in our patients could have changed from those used for patients in earlier reviews. Nevertheless, we found few differences between our patients and those in two reviews from the United States before 1967: 199 hospitalized patients in San Francisco, Calif, from 1947 to 1958,[5] and 190 hospitalized and clinic-treated patients in Dallas from 1959 to 1966.[6] In these series, 57% and 43% of patients were less than 1 year of age, and virtually all infants in this age group were hospitalized. Eighty-four percent and 67% of the children had had no pertussis vaccine, respectively. The rates of paroxysmal cough (85%), fever (26%), vomiting (70%), and convulsion (5%),[5] and the distribution of total white blood cell counts and mean percent of lymphocytes,[5,6] were similar to those found in the present review. Other complications of pertussis, eg, encephalopathy,[20] apnea, epistaxis, melena, and weight loss,[6] were not quantitated. The rates of primary pneumonia caused by pertussis also were difficult to assess because criteria for this diagnosis were likely to be subjective and to vary.[21] However, the mortalities were 1.5% and 1.6%, respectively, and pneumonia and/or severe hypoxia caused or contributed to the death of five and three infants, respectively, of the six patients (total) who died.[5,6] These rates were almost identical to those of patients in our review.

The patients in our series differed from those in the previous reports in at least two respects. They had a substantially shorter mean hospital stay than those described by Kaufman and Bruyn[5] (7.4 vs 16 to 18 days). Our patients also were more likely to be exposed to an ill, coughing adult (44% of patients with a known contact) than patients described by Kaufman and Bruyn (4% of patients with a known contact). A shift in the proportion of exposures from an ill child to an ill adult was recognized previously in Dallas, occurring between 1965 and 1971,[13] and is consistent with reports of increasing numbers of cases recognized in young adults.[2]

Available whole-cell pertussis vaccine is effective in reducing the incidence and severity of pertussis. The protective efficacy of this vaccine is estimated to be only 60% to 70% after two doses and increases to 80% to 90% after three doses.[22] We found that infants younger than 3 months had the highest rates of complications. Unfortunately, most patients were too young to have received sufficient doses of vaccine to assess the effect of the number of doses on the rates of complications.

The concern of a possible relationship between encephalitis and pertussis vaccination has decreased acceptance of pertussis vaccines.[23] Outbreaks of pertussis after a decrease in the use of these vaccines have been demonstrated in the United Kingdom,[24,25] Japan,[26] and Sweden.[11] The overall benefit and cost-effectiveness of whole-cell pertussis vaccine have been reviewed and well defined.[27,28] The patients described herein demonstrate that pertussis continues to be a serious illness with measurable mortality, despite advances in supportive care. Secondary bacterial pneumonia was the major cause of death. It is important that physicians not grow lax in emphasizing the serious nature of the disease and the benefits of vaccination at as young an age as possible.

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Diurnal Variation in the Pharmacokinetics and Myelotoxicity of Mercaptopurine in Children With Acute Lymphocytic Leukemia

Gideon Koren, MD; Anne Marie Langevin, MD; Nancy Olivieri, MD; Ester Giesbrecht, MSc;
Alvin Zipursky, MD; Mark Greenberg, MD

• During their maintenance therapy, children with acute lymphoblastic leukemia are treated with a daily dose of mercaptopurine for several years. A recent retrospective analysis has suggested that administration of the drug in the evening results in a better prognosis. We compared the disposition pharmacokinetics of mercaptopurine administered in the morning vs in the evening in 13 children with acute lymphoblastic leukemia. Elimination half-life of mercaptopurine was significantly longer in the evening than during the day (423 ± 142 minutes vs 176 ± 22 minutes, mean ± SEM). The area under the concentration-time curve ($AUC_{0-\infty}$) was significantly larger in the evening (24 713 ± 3536 ng/mL per minute vs 17 120 ± 1474 ng/mL per minute). These differences were even more pronounced when comparing the area under the curve of the postdistributive phase ($AUC_{300\ min-\infty}$, 7724 ± 2955 ng/mL per minute in the evening vs 2597 ± 712 ng/mL per minute during the day). In a second study, 12 children with acute lymphoblastic leukemia receiving mercaptopurine in the morning had their medication administration switched to the evening. Within 2 weeks there was a sharp fall in peripheral white blood cell counts in all patients (from 4.1 × 10^9/L to 2.2 × 10^9/L) mainly due to a drop in polymorphonuclear lymphocytes (from 2.78 × 10^9/L to 1.05 × 10^9/L). We conclude that the diurnal variations of mercaptopurine disposition result in clinically important myelotoxicity of the drug.

(*AJDC.* 1990;144:1135-1137)

Acute lymphoblastic leukemia (ALL) is the most common form of pediatric cancer, diagnosed in 1 of every 40 000 children per year. During the last 2 decades, there has been substantial improvement in the prognosis of this disease, and at present, low-risk patients have cure rates of up to 90%. More than 90% of children achieve complete remission, 20% to 40% eventually relapse during maintenance therapy; relapsing patients are much more likely to succumb to their illness.[1] Maintenance therapy for most low-risk children usually includes a daily oral dose of mercaptopurine (75 mg/m²) and a weekly dose of methotrexate (20 mg/m²) given either orally, intravenously, or intramuscularly, according to different protocols.

Several recent studies have suggested that variability in the pharmacokinetics of these two drugs may affect clinical response and eventually outcome. Evans et al[2] have shown that relapsing children have significantly faster clearance rates of methotrexate and, therefore, are exposed to substantially lower serum concentrations of the drug. We have shown that relapsing patients receive significantly less methotrexate during the first and second years of therapy.[3] Zimm and colleagues[4] have documented very low and underpredictable oral bioavailability of mercaptopurine and in some patients concentrations of the drug are even undetectable.[5]

In a recent retrospective analysis, Rivard et al[6] documented better prognosis of ALL in children receiving their maintenance chemotherapy in the evening vs those treated in the morning; however, no attempt was made to investigate the mechanism(s) underlying this phenomenon. During the last decade, important diurnal variations in the disposition of several drugs have been documented, including theophylline and benzodiazepines.[7,8] In this study, we compared the pharmacokinetic disposition of mercaptopurine given orally in the morning vs in the evening, in an attempt to identify a mechanism leading to better outcome following evening therapy. Subsequently, we assessed changes in peripheral white blood cell (WBC) counts in children with ALL whose treatment was switched to evening administration.

PATIENTS AND METHODS

Pharmacokinetic Studies

Thirteen children (4 girls and 9 boys) with ALL participated in the pharmacokinetic studies; 10 patients completed both day and evening studies dies, whereas 2 underwent only the evening study; and 1, only the day study. Their ages ranged from 4 to 11.5 years (mean 6.5 ± 2.4 years).

At the time of the studies all the patients were in complete remission for periods of 3 to 16 months and received their maintenance therapy in the morning, which included a daily oral dose of 75 mg/m² of mercaptopurine and a weekly oral dose of 20 mg/m² of methotrexate. Monthly pulses of vincristine sulfate and prednisone were given intravenously. For prophylaxis against *Pneumocystis carinii* they received trimethoprim and sulfamethoxazole. None had received any additional medications during the previous month and had not suffered from an intercurrent illness. After approval by our Human Experimentation Review Committee and with written parental consent, the children were randomized to be studied either first in the evening or during the day in our chemotherapy unit.

After at least an 8-hour fast, the children

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From the Divisions of Clinical Pharmacology (Dr Koren) and Hematology-Oncology (Drs Langevin, Olivieri, Zipursky, and Greenberg), Department of Pediatrics, the Department of Biochemistry (Ms Giesbrecht), and The Research Institute, The Hospital for Sick Children, Toronto, Departments of Pediatrics (Drs Koren, Olivieri, Zipursky, and Greenberg) and Pharmacology (Dr Koren), The University of Toronto, Canada.

Reprint requests to Division of Clinical Pharmacology, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (Dr Koren).

received mercaptopurine (75 mg/m^2 orally) with water. Complete administration of the dose was supervised by one of the investigators. Through an indwelling venous catheter, blood samples were drawn just before drug administration and then at 10, 20, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes following the mercaptopurine dose. Samples were centrifuged and serum samples were separated and stored at −20°C until analyzed within 1 week. The second study (day or evening) took place 2 to 4 weeks later.

Serum concentrations of mercaptopurine were measured by a high-performance liquid chromatography developed in our laboratories.[9] The lowest sensitivity of this assay is 1 ng/mL and the coefficient of variation within the measured range (3 to 300 mg/mL) is less than 5%.

Using the nonlinear ADAPT program,[10] the following pharmacokinetic values were generated: elimination half-life, area under the curve (AUC) of concentration time $AUC_{0\text{-}480}$, $AUC_{0\text{-}\infty}$, and $AUC_{800\text{-}\infty}$ corresponding to the postdistributive phase.

Myelotoxicity Studies

Twenty children with ALL were studied to record the potential effects of switching mercaptopurine therapy from morning to evening on hemoglobin, platelet count, WBC count, and polymorphonuclear (PMN) counts. The ages of the patients studied were between 4 and 12 years (mean 6 ± 2.1 years); they were 2 to 18 months into maintenance therapy. Of these children, 8 were excluded because within 2 weeks of switching mercaptopurine therapy from morning to evening, other changes in chemotherapy took place (n = 4) or because they had had unstable levels of WBCs and PMNCs in the 3 months prior to the switch or exhibited a decrease or increase in WBC or PMN counts before changing the mercaptopurine treatment schedule from morning to evening (n = 4). Compliance was verified by history during the clinic visit.

Pharmacokinetic and hematologic values were compared between the morning and evening studies using nonparametric statistics (Wilcoxon's or Mann-Whitney *U* tests whenever appropriate); data are expressed as mean ± SEM.

RESULTS

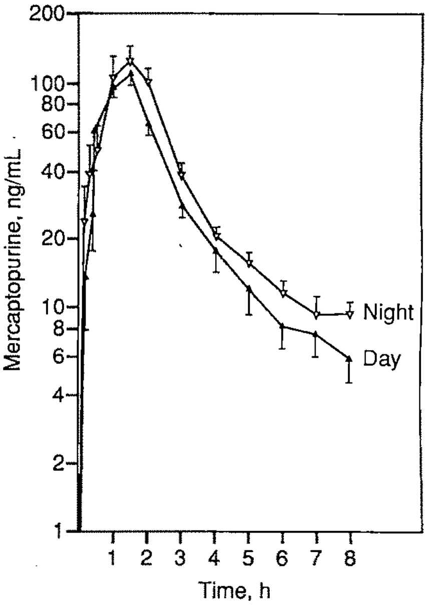
Serum concentrations of mercaptopurine were consistently higher in the evening, yielding larger AUCs (Figure). The $AUC_{0\text{-}\infty}$ of the 10 children serving as their own controls was 22 566 ± 5556 ng/mL per minute in the evening and 13 549 ± 2843 ng/mL per minute during the day ($P = .08$, Wilcoxon's). Adding the data from children studied only in the evening or only during the day yields an AUC of 24 713 ± 5353 ng/mL per minute (in the evening) and 17 120 ± 1474 ($AUC_{0\text{-}\infty}$) ng/mL per minute (in the morning), respectively ($P < .05$, Mann-Whitney *U*). In three children studied both in the morning and in the evening, the $AUC_{0\text{-}\infty}$ in the evening was more than 100% larger than during the day. Differences in AUC were more pronounced when looking at only the postdistributive phase ($ACU_{800\text{-}\infty}$ of 7724 ± 2955 ng/mL per minute [evening] vs 2597 ± 712 ng/mL per minute [morning]; [$P < .01$]). Elimination half-life of mercaptopurine was 423 ± 142 minutes in the evening and 176 ± 22 minutes in the morning ($P = .02$). Differences between the morning and evening studies were detected also in time-to-peak; time-to-peak was longer in the evening in 5 patients, equal in the morning and in the evening in 4 patients, and shorter in the evening in 1 patient.

Within 2 weeks of changing the treatment schedule from morning to evening, all 12 children experienced a decrease in WBC count (from 4.1 ± 0.4 × 10^9/L to 2.2 ± 0.33 × 10^9/L; $P < .005$) and in PMN count (from 2.78 ± 0.34 × 10^9/L to 1.05 ± 0.2 × 10^9/L; $P < .0005$). Patients experienced a slight decrease in hemoglobin (147 ± 4.7 g/L to 106.3 ± 4.4 g/L; $P < .05$) with no apparent changes in platelet counts (280 ± 24 × 10^9/L and 316 ± 42 × 10^9/L respectively; $P > .1$).

Subsequently, chemotherapy had to be discontinued in 9 children, 2 of whom were hospitalized and treated with broad-spectrum antibiotics for fever accompanying the neutropenia, and a third had fever and otitis. Chemotherapy was withheld in these 9 children for periods of 7 to 30 days; thereafter, the dose had to be reduced by 20% to 25% in 7 children, whereas an eighth child's treatment was switched back to the orignal dose received in the morning and the ninth child's treatment was restarted on the same dose, exhibiting relative neutropenia (WBC count, 2.4 × 10^9/L; PMN count, 1.68 × 10^9/L).

COMMENT

The disposition of mercaptopurine is subjected to appreciable interpatient variation; the AUC achieved with a standard dose may vary manyfold and in some patients serum concentrations are undetectable.[5] Because children with leukemia are administered 75 mg/m^2 for several years without modification of the dose according to achieved serum concentrations, it is conceivable that they are exposed to very different amounts of mercaptopurine over time. It is not yet known whether such differences may affect the outcome of this malignancy, but data on methotrexate clearly show that children with higher clearance rates, and therefore lower systemic exposure, are more likely to relapse and to succumb to their illness.[2]



Mean concentration time curve of mercaptopurine given in the morning vs the evening to children with acute lymphoblastic leukemia.

During the past decade, the effects of diurnal variation on the disposition and pharmacodynamics of drugs have been recognized. In the case of theophylline, half-life has been shown to be longer in the evening and the absorption of sustained released preparations is slower.[7] In the case of triazolam, elimination half-life is significantly longer after evening administration, and so is the absorption half-life and absorption lag time.[8]

The first part of our study aimed at detecting possible changes in the disposition pharmacokinetics of mercaptopurine administered orally in the standard dose of 75 mg/m^2. We have demonstrated that children are exposed to significantly larger amounts of mercaptopurine after receiving the drug in the evening. Because only the oral dose is studied, it is impossible to analyze whether these changes stem from higher oral bioavailability, smaller distribution volume, decreased clearance rate, or a combination of the above. The fact that elimination half-life is prolonged in the evening may suggest decrease in the metabolism of mercaptopurine, with or without changes in distribution volume.

The low oral bioavailability of mercaptopurine is the result of first-pass metabolism of the drug by intestinal and liver xanthine oxidase that can be inhibited by concomitant administration of allopurinol.[11] It is potentially possible that diurnal variation in xanthine oxidase activity may participate in the diurnal phenomenon. The prolonged time-to-peak observed in the evening in half of our patients may suggest retarded absorption of the drug from the gastrointestinal tract, potentially due to changes in intestinal motility. The delay in achieving peak concentrations in the evening is consistent with studies of other drugs; it has been shown that posture, per se, prolongs the rate constant of absorption, resulting in a longer lag time before absorption.[12] In the present studies, the patients were allowed to be active during the day, whereas during the evening, all of them lay in bed and fell asleep within several hours of study.

Our studies document that the AUC$_{0-\infty}$ of mercaptopurine, reflecting total systemic exposure to the drug, is significantly larger after an evening dose. In some of our patients these differences were as large as twofold or threefold. This subgroup may correspond to the three children in our subsequent clinical studies who had neutropenia and fever secondary to evening administration of the drug. It is potentially important that the differences in AUCs were much more pronounced when comparing the postdistributive phase, with the mean exposure being threefold higher. It may be that the prolonged terminal low concentrations of mercaptopurine are more important in exerting the pharmacodynamic effect of this antimetabolite, as they reflect postabsorption and postdistribution equilibrium. Our studies included children aged 4 to 10 years, so there were no young children or adolescents having a poor prognosis. To the best of our knowledge, there is no evidence that mercaptopurine pharmacokinetics are age related within the pediatric age group.

The decision to switch our patients' administrations from daily to nightly maintenance therapy followed the retrospective analysis that showed better survival in children receiving their maintenance therapy in the evening.[6] The subsequent decrease in peripheral WBC count, mainly due to neutropenia, is consistent with the significantly higher exposure to mercaptopurine after evening administration. In three of our patients, myelotoxicity resulted in hospitalization and intravenous antimicrobial therapy. In a recent study, the mean WBC count during maintenance therapy was found to be significantly related to risk of hematologic relapse, giving patients with the higher cell count the poorer outcome.[13] It can be argued that the diurnal effect on WBC and PMN counts may reflect improved compliance during the evening studies. It is possible that patients were more compliant once enrolled into the experimental aspect of the evening study. Judging by parental reports, it does not appear that compliance changed; however, such reports have been shown not to reflect avidly true compliance with mercaptopurine among patients with ALL.[14] Because cellular protein synthesis is more pronounced during the evening, it is possible that other diurnal changes contribute to the observed myelotoxicity.[6]

Our studies support the retrospective observation and suggest that nightly therapy with mercaptopurine produces more favorable results by increasing the effectiveness of the drug.[6] Our results further suggest that interpatient variation in disposition pharmacokinetics of mercaptopurine may be an important determinant of survival of ALL children. If prolonged low concentrations of mercaptopurine are needed to maintain an antileukemic effect, then one should ask why a drug with such a short elimination half-life is administered once daily. To date, no studies have addressed the potential efficacy of a divided mercaptopurine dose given more than once daily.

A prospective study is needed to verify better survival of children receiving mercaptopurine in the evening; however, the clinician should be aware of the potentially dangerous myelotoxicity that may result.

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Adult Height Achieved in Children After Kidney Transplantation

Carsten Aschendorff, MD; Gisela Offner, MD; Lothar Winkler, MD;
Eckhart Schirg, MD; Peter F. Hoyer, MD; Johannes Brodehl, MD

• We evaluated posttransplantation growth, bone maturation, and adult height in 20 adolescents who had received kidney transplants at the age of 10.5 to 17 years. Nine patients (five male, four female) were treated with cyclosporine and low-dose prednisolone, and 11 children (six male, five female) were treated with azathioprine and high-dose prednisolone. The cumulative dose of steroids after transplantation was significantly lower in the cyclosporine-treated group. Bone age, according to the radius-ulna-short bones method of Tanner and Whitehouse, was almost the same in both groups at the time of transplantation (15.0 and 14.6 years for male subjects, 13.3 and 13.1 years for female subjects). Predicted adult height (Tanner-Whitehouse Mark II-method of Tanner et al) and target height were estimated at transplantation. Adult height was defined as achieved when bone age in male subjects had reached 18 years and, in female subjects, 16 years. Bone maturation of the cyclosporine-treated patients occurred at a normal rate (0.92 bone-age years per chronologic year), whereas the azathioprine-treated group exhibited a significantly slower rate (0.56 bone-age years per chronologic year). The growth rate per year for the cyclosporine-treated group was more than double that of the azathioprine-treated group (3.0 cm vs 1.4 cm). The adult height of the cyclosporine-treated group exceeded the predicted adult height by a mean of 1.3 cm, but the azathioprine-treated group missed it by 3.9 cm. Target heights could not be achieved in any group. Kidney function was significantly lower in the cyclosporine- vs the azathioprine-treated group, but no patients suffered from severe renal insufficiency. We conclude that cyclosporine and low-dose prednisolone are associated with normal bone maturation and a better prognosis for final height in children with renal transplants.

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Growth retardation is one of the major problems of chronic renal failure in childhood, especially during dialysis.[1-4] The aims of kidney transplantation in children are independence from dialysis and full rehabilitation, including normal growth and development. The reduction of the dose of steroids in the immunosuppressive regimen by use of cyclosporine leads to an improved growth rate after kidney transplantation when compared with conventional treatment with azathioprine and high-dose corticosteroids.[5-8] The effect on the patients' final height in adulthood is unknown.

We compared linear growth, bone maturation, and adult height retrospectively in 20 adolescents who received kidney transplants between 1974 and 1986 and were treated either with cyclosporine and low-dose prednisolone or with azathioprine and high-dose prednisolone.

SUBJECTS AND METHODS

We studied 20 patients (nine female and 11 male) who had received renal allografts at the Medizinische Hochschule, Hannover, West Germany, between 1974 and 1986 and had reached adult height by the end of 1988. Adult height was defined as achieved when the bone age of male adolescents had reached 18 years and that of female adolescents, 16 years. Bone age was determined by the radius-ulna-short bones method of Tanner and Whitehouse, using a roentgenogram of the left hand and wrist.[9] At the time of transplantation, the male patients had a bone age of 13 to 16 years, and the female patients of 11 to 14 years. Subjects with bone ages lower than 13 and 11 years, respectively, and those with nephropathic cystinosis were excluded because of their extreme growth retardation for chronologic and bone age.

Chronologic and bone age at the time of transplantation and other data concerning kidney transplantation and immunosuppression are listed in Table 1. The cyclosporine-

Table 1.—Number of Patients, and Chronologic and Bone age, at Time of Transplantation, and Origin and Number of Grafts

	Cyclosporine (n=9)	**Azathioprine (n=11)**
Year of transplantation	1982-1986	1974-1982
Male patients		
No.	5	6
Mean chronologic age, y (range)	15.5 (13.0-16.9)	14.5 (12.6-16.9)
Mean bone age, y (range)	15.0 (13.7-15.9)	14.6 (13.4-15.9)
Female patients		
No.	4	5
Mean chronologic age, y (range)	14.0 (12.0-16.0)	13.0 (10.5-15.8)
Mean bone age, y (range)	13.3 (12.9-13.7)	13.1 (12.4-14.0)
Living related/cadaveric grafts	1/8	4/7
No. of patients with first/second/third graft	7/0/2	11/0/0

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From the Department of Pediatric Nephrology and Metabolic Disorders, Children's Hospital (Drs Aschendorff, Offner, Winkler, Hoyer, and Brodehl), and the Department of Radiology (Dr Schirg), Medical School of Hannover, Hannover, West Germany.

Reprint requests to Abteilung für Pädiatrische Nephrologie und Stoffwechselerkrankungen, Kinderklinik, Medizinische Hochschule, Konstanty-Gutschow-Str 8, D-3000 Hannover 61, Federal Republic of Germany (Dr Aschendorff).

treated group consisted of five male and four female patients, the azathioprine-treated group of six male and five female patients.

The original diseases of the patients were about the same in both groups: congenital-familial diseases in four of nine cyclosporine-treated and five of 11 azathioprine-treated patients. The details of the two immunosuppressive protocols are given in Table 2.[10,11]

At the time of transplantation, the predicted adult height was calculated, according to the formula of Tanner and coworkers,[12] from the body height and chronologic and bone ages (Tanner-Whitehouse Mark II-method). The target height was calculated from the mean parental height plus or minus 6.5 cm for male and female adolescents, respectively. Standing height was measured with a stadiometer at the time of transplantation and when adult height was reached.

The glomerular filtration rate (GFR) was calculated at both times from the serum creatinine levels and standing height according to the formula of Schwartz et al.[13] The calculated GFR correlates well with the inulin clearance value, even in children who have received transplants (Hoyer et al[14]). The trinitrophenol (picric acid) method was used for the determination of creatinine levels with an analyzer (Kreatinin, Beckmann, Munich, West Germany). Investigations were performed with the informed consent of patients and their parents.

For statistical analysis, Student's *t* test and the nonpaired Mann-Whitney *U* test were used in conjunction with computer system software (SPSS-X, SPSS Benelux, Gorinchen, the Netherlands).

RESULTS

The chronologic age when adult bone age was reached under the two immunosuppressive regimens is listed in Table 3. In both sexes, the mean chronologic age was higher with azathioprine and high-dose prednisolone than with cyclosporine: 20.1 vs 18.7 years in male patients and 19 vs 17.4 years in female patients. The duration between transplantation and achieved adult bone age was almost twice as long in the azathioprine-treated group as in the cyclosporine-treated group, although bone age at the time of transplantation was nearly the same in both groups. The mean difference in duration is statistically significant in male subjects (5.6 vs 3.2 years; $P<.01$) and weakly significant in female subjects (6.0 vs 3.4 years; $P<.05$).

Table 2.—Two Different Immunosuppressive Regimens Used in Pediatric Kidney Transplantation

	Immunosuppressive Agent, Daily Dose	Daily Prednisolone, mg/kg (mg/m^2)
	Regimen 1	
	Azathioprine, mg/kg	**High-Dose Prednisolone**
Intraoperatively	3	10 (300)
Days 1-3	3*	10 (300)
Day 4 to week 3	3*	3 (90)
Weeks		
4-5	3*	2 (60)
6-8	3*	1 (30)
9-12	3*	0.5 (15)
After 1 y	3*	5-10 mg absolute
	Regimen 2	
	Cyclosporine, mg/m^2 (Orally)	**Low-Dose Prednisolone**
6 h preoperatively	500	...
Intraoperatively (intravenously)	...	10 (300)
Week		
1	500†	2 (60) orally
2	450†	1 (30)
3	400†	0.5 (15)
4	350†	0.4 (12)
5	300†	0.3 (9)
6	300†	0.2 (6)
7 and afterward	300†	0.13 (4)

*Therapy discontinued if leukocyte count is below 3.0×10^9/L.

†Administered in two doses per day and adjusted to trough blood levels of 150 to 200 ng/mL.

Table 3.—Chronologic Age and Duration of Growth After Transplantation Until Adult Bone Age Was Reached*

	Cyclosporine	Azathioprine	P
Male patients			
No.	5	6	...
Age at adult height, y	18.7±1.5	20.1±1.2	...
Time of growth, y	3.2±1.1	5.6±1.2	<.01
Female patients			
No.	4	5	...
Age at adult height, y	17.4±1.2	19.0±1.7	...
Time of growth, y	3.4±0.6	6.0±1.9	<.05

*Male patients' adult bone age was determined at 18 years, female patients' bone age at 16 years. Values are mean±SD. *P* values are by Student's *t* test.

The maturation of bone age per year after transplantation calculated for male and female subjects together showed a nearly normal development in the cyclosporine-treated group, with a mean value of 0.92±0.28 bone-age years per chronologic year, in contrast to the azathioprine-treated group, with a value of 0.56±0.13 bone-age years per chronologic year ($P<.01$).

The values for height at the time of transplantation and the final heights are listed in Table 4. Both male and female subjects showed an absolute growth of 10 cm under cyclosporine treatment. With azathioprine, the male subjects grew only 8 cm and the female subjects 7 cm. This reflects a significantly better growth rate of both sexes in the cyclosporine-treated patients (3.0±1.3 vs 1.4±0.8 cm/y; $P<.01$).

In Table 4, the achieved adult heights were also compared with the predicted adult heights and the target heights,

Table 4.—Height at Time of Transplantation, Predicted and Target Heights, and Achieved Adult Heights*

	Cyclosporine	Azathioprine
Male patients		
No.	5	6
Height at transplantation, cm	164±10	159±12
Predicted adult height, cm	175±4	171±9
Target height, cm	178±7	182±7
Adult height, cm	174±4	167±10
Female patients		
No.	4	5
Height at transplantation, cm	151±11	149±6
Predicted adult height, cm	158±12	160±5
Target height, cm	168±10	165±3
Adult height, cm	161±12	156±7

Table 5.—GFR and Plasma Creatinine Shortly After Transplantation and at Time of Reaching Adult Height*

	Cyclosporine (n=9)	Azathioprine (n=11)	*P*
GFR, mL/min per 1.73 m²			
Transplantation	51±16	83±23	<.01
Adult height	39±10	66±15	<.001
Plasma creatinine, µmol/L			
Transplantation	132±56	78±32	<.05
Adult height	177±50	97±21	<.01

*GFR indicates glomerular filtration rate. Values are mean±SD. *P* values are by Student's *t* test.

Table 6.—Total Dosage of Prednisolone Received in First 4 Years After Transplantation*

Years After Transplantation	Cyclosporine	Azathioprine	*P*
1			
No. of patients	9	11	...
Total dosage	140±66	398±123	<.001
2			
No. of patients	9	11	...
Total dosage	45±30	85±29	<.01
3			
No. of patients	7	11	...
Total dosage	38±28	72±27	<.05
4			
No. of patients	6	11	...
Total dosage	32±6	59±18	<.01

*Dosage values are mean±SD in milligrams per kilogram of body weight per year. *P* values are by Student's *t* test.

which were both determined at the time of transplantation. Under cyclosporine treatment, the female subjects exceeded their predicted height by a mean of 3 cm, and the male subjects under the same treatment almost reached predicted heights. Under azathioprine treatment, the predicted height was not reached. Target height exceeded adult height in both groups.

The differences between the predicted adult height and the achieved adult height showed a significantly better result in the cyclosporine-treated group compared with the azathioprine-treated group (+1.3±3.2 vs −3.9±3.9 cm; *P*<.01).

Because chronic renal failure of the engrafted kidney would determine the growth rates, the values for GFR and plasma creatinine are given in Table 5. In both groups, the GFR ranged between 26 and 119 mL/min per 1.73 m² for a short time after transplantation and declined to 24 to 88 mL/min per 1.73 m² by the end of the study. The cyclosporine-treated group showed a significantly lower GFR at both times, but no patient suffered severe renal insufficiency (Table 5).

The cumulative dose of steroids resulting from the immunosuppressive protocols and additional steroid pulses given against acute rejection was significantly lower in the cyclosporine-treated group in the first 4 years after transplantation (Table 6). The total number of steroid pulses was the same in both groups. All steroid pulses were given within the first 3 years after transplantation (16 therapeutic sessions with 76 pulses total in both groups).

COMMENT

It is well accepted that high dosages of corticosteroids (more than 6.0 mg/m² per day of prednisolone) lead to growth retardation, which is also true in children with renal transplants[15-17] who no longer suffer from renal failure. As previously shown by our group and others, cyclosporine combined with low-dose corticosteroids offers a normal yearly growth rate after kidney transplantation.[5,18] The effect of such treatment on the bone maturation and the adult height is unknown.

Prediction of adult height is difficult in children suffering from chronic disease, in whom the grade of growth and bone-age retardation depends on the duration of renal insufficiency and the type of underlying kidney disease.[19,20] The radius-ulna-short bones method of Tanner and Whitehouse calculates the bone age using a point system for the maturation of single bones and epiphyseal plates. It is more precise than the method of Greulich and Pyle,[21] where bone age is determined only by comparison of full roentgenograms of the left hand and wrist with an atlas. The disadvantage of the Tanner-Whitehouse Mark II-method for adult height prediction is a slight overprediction, when there is a marked bone age retardation for chronologic age.[22-24] Therefore, we restricted our patients to a limited range of bone age at the time of transplantation and excluded patients with cystinosis. Considering these restrictions, the Tanner-Whitehouse Mark II-method using the radius-ulna-short bones method bone age is a reliable prediction method.[25]

In our study, the cyclosporine-treated patients showed no acceleration in bone maturation. Their epiphyses closed at a normal age, considering the retardation of bone age at the time of transplantation, and the patients reached their predicted adult height.

In contrast, the azathioprine-treated patients demonstrated a delay in bone maturation and had lower growth rates. This led to a further growth retardation for chronologic age and was only partially compensated by a longer growth period. Therefore, they could not reach their predicted adult height, although their renal function was better than that of the cyclosporine-treated patients.

The difference in the total amount of steroids received underlines the importance of low-dose prednisolone treatment for growth and development. We conclude that cyclosporine offers a better outlook than azathioprine plus high-dose prednisolone for final height in children undergoing transplantation.

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Pediatric Trauma Score: Predictor of Hospital Resource Use?

Charles Aprahamian, MD; Richard P. Cattey, MD; Alonzo P. Walker, MD; Harvey W. Gruchow, PhD; Gary Seabrook, MD (*Arch Surg*. 1990;125:1128-1131)

Failure to Recognize Fetal Alcohol Syndrome in Newborn Infants

Bertis B. Little, MA, PhD; Laura M. Snell, MPH; Charles R. Rosenfeld, MD;
Larry C. Gilstrap III, MD; Norman F. Gant, MD

• A clinically distinct constellation of major and minor anomalies, termed the *fetal alcohol syndrome*, occurs among infants whose mothers abuse alcohol during pregnancy. In addition, significantly higher rates of pregnancy complications, including perinatal deaths and fetal growth retardation, occur among these women and their offspring. We studied the medical records of 40 infants born to 38 alcohol abusers and the frequency of characteristics associated with fetal alcohol syndrome. Physical examinations of 6 infants revealed primary features consistent with a diagnosis of fetal alcohol syndrome. Postnatal growth and development were very poor in 17 (50%) of 34 liveborn alcohol-exposed infants. The diagnosis of fetal alcohol syndrome did not appear in the medical records of any of these infants despite the fact that the mothers' obstetric records included a history of alcohol abuse during pregnancy. This finding emphasizes the importance of good communication between obstetric and pediatric medical staff at this hospital, particularly when providing care for pregnant women and newborn infants at high risk for complications due to maternal alcohol or other drug abuse.

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Fetal alcohol syndrome (FAS) is caused by maternal alcohol abuse during pregnancy, and its characteristic pattern of minor facial anomalies (facies) is readily reproduced in rodent and nonhuman primate animal models.[1] Infants with FAS are characterized by prenatal and postnatal growth deficiency, mental retardation (often profound), behavioral disturbances, and typical facies (flattened nasal bridge, hypoplastic to absent philtrum, narrow forehead, etc).[2] The ability to recognize this syndrome varies according to the physician's skills and interest in dysmorphologic features; thus, the estimated prevalence rates for FAS among populations are directly affected by such ascertainment biases.

The diagnosis of FAS is made easier by a known maternal history of alcohol abuse, but the syndrome should be recognizable by observers unaware of the mother's drinking status. Studies using examiners "blinded" to the mother's alcohol consumption patterns are difficult to implement and often fail to distinguish infants born to mothers who drank heavily during pregnancy.[3,4] Moreover, trained observers frequently have difficulty in agreeing on a diagnosis.[3] Less severe effects of maternal alcohol use during pregnancy include mild to moderate mental and physical growth retardation, known collectively as fetal alcohol effects (FAE).[5] Confounding variables, such as interviewer bias, inconsistencies in diagnosis of FAS and FAE, ethnicity, socioeconomic status, nutrition, and other substance abuse, make it difficult to interpret data regarding the relationship between the amount of alcohol consumed and FAS or FAE.

In this study, we analyzed the underdiagnosis of FAS and FAE, as indicated by clinical information recorded in the maternal and infant medical records, in one of the largest neonatal services in the United States.

MATERIALS AND METHODS

Medical records of women who reported abusing alcohol during pregnancy were identified using a large validated, prospectively collected database (MANDATE) that contained information on more than 28 000 deliveries from September 1977 to December 1980. This data management system was designed to gather, validate, and organize information related to maternal and neonatal care in Dallas County, Texas. Data were collected by trained research nurses and recorded on forms, which were read by an optical scanner onto a computer system disk file. Audits were performed at quarterly intervals to assess the accuracy of randomly selected charts. The error rate was 1% to 2% for data recording and less than 1% for data entry into the computerized database.[5] Information regarding alcohol use was available for 5602 women who delivered at Parkland Memorial Hospital, Dallas, Tex. This county teaching hospital serves a low-income/indigent population in a large metropolitan area and in 1977 performed one third of the deliveries in the county.

Alcohol intake information for all infants purportedly exposed to alcohol in utero in the database ($n = 38$) was verified with the medical records, and no discrepancies were found.[6] Alcohol abuse was defined as drinking four or more alcoholic beverages per day. Information was abstracted from the medical charts of these women regarding the amount of alcohol used during pregnancy, pregnancy outcome, and other substances used. Medical records of infants born to these women were also abstracted for information about health status, the pediatric examination findings at birth, and perinatal complications. The infants' medical records at Parkland Memorial Hospital and Children's Medical Center, an adjacent pediatric referral hospital for North Texas, were also reviewed to assess postnatal growth and development. A comparison group of 80 mothers and their respective infants was randomly selected from 5564 women who did not drink during pregnancy, and similar data were abstracted from their medical records.

In this study, estimated gestational age (EGA) was calculated from the mother's last menstrual period. Fetal growth retardation (FGR) was defined (1) by diagnosis in the medical records or (2) as a birth weight less than or equal to the 10th percentile for EGA-specific reference data. Microcephaly was defined in the same fashion as FGR. Birth weight, birth length, neonatal head circumference, EGA, and other clinical observations were abstracted from the newborn examination records. Measurements were compared with the discharge records and the MANDATE database for verification.

χ^2 Analysis and the odds ratio (OR) determination with 1 *df* and Yates' correction for small sample sizes were performed using the Centers for Disease Control (Atlanta, Ga) Statistical Analysis Package. Analysis of variance (ANOVA) and analysis of covari-

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From the Departments of Obstetrics and Gynecology (Drs Little, Gilstrap, and Gant), Family Practice and Community Medicine (Ms Snell), and Pediatrics (Dr Rosenfeld), The University of Texas Southwestern Medical Center at Dallas.

Reprint requests to the Department of Obstetrics and Gynecology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75235-9032 (Dr Little).

Table 1.—Alcohol Abuse Levels of Mothers

Drinks per Day	No. (%)
0	80 (100)
4-5	23 (61)
6-7	8 (21)
≥8	7 (18)
Total Nondrinkers	**80 (100)**
Total Drinkers	**38 (100)**

ance (ANCOVA) were performed using SPSS.[7] The multiple statistical comparisons in the present study raise the possibility that as many as three significant associations may have occurred by chance. The Bonferroni theorem indicates that $P<.001$ should be used to correct for the number of multiple comparisons to obtain an adjusted $P<.05$.[8]

RESULTS

Medical records of 38 (0.7%) of the total 5602 women surveyed reported a history of alcohol abuse during pregnancy. Forty infants were born to this group, including two sets of twins. One twin from one set was stillborn, and one from the set during the neonatal period. Hence, 38 infants were available for further study. Eighty-one infants, including one set of twins (1 emaciated fetal death and 1 liveborn), were born to the 80 women in the comparison group. Mean maternal age in the study group was 23.3 years (range, 16 to 38 years) compared with 21.3 years (range, 16 to 35 years) for the control group ($P<.05$). Both groups had a mean of 2.1 living children before the present birth. Forty-five percent of the study patients were black, 34% were white, and 21% were Hispanic. The study group had significantly more white women than did the control group and the patient population at large ($P<.01$).[9]

Of the 38 women who drank at least four alcoholic beverages per day, 15 (39%) drank six or more alcoholic beverages per day during pregnancy (Table 1). Significantly more mothers who abused alcohol during pregnancy also reported using other substances (Table 2) and indicated syphilis as a primary pregnancy complication (Table 3). Neonatal outcome was not significantly poorer in the 34 offspring of mothers who abused alcohol ($P>.05$) (Table 4).

Estimated gestational age was significantly lower in the pregnancies of alcohol abusers. Size at birth (ie, birth weight, length, and head circumfer-

Table 2.—Other Substances Used During Pregnancy

Substance	No. (%) by Alcohol Use During Pregnancy: Drinkers (n=38)	Nondrinkers (n=80)	P (OR)*
Tobacco	23 (61)	9 (11)	<.001 (12.1)
Amphetamines	6 (16)	0	<.001
Heroin	6 (16)	0	<.001
Marijuana	5 (13)	0	<.04
Preluden	4 (11)	0	<.02
Hydroxyprogesterone caproate (Delalutin)	3 (8)	0	NS
Prescribed drugs	2 (5)	4 (5)	NS
Methaqualone (Quaalude)	2 (5)	0	NS
Cocaine	1 (3)	0	NS
Toluene	1 (3)	0	NS
Methadone	1 (3)	0	NS
"Ts and blues"†	1 (3)	0	NS
Diazepam (Valium)	1 (3)	0	NS

*OR indicates odds ratio; NS, not significant.

†"Ts and blues" refers to a mixture of pentazocine (Talwin) and blue-colored antihistamine tablet, tripelennamine (Pyribenzamine), that is made by crushing tablets of both drugs and dissolving in water for intravenous injection.

Table 3.—Maternal Pregnancy Complications*

Complication	No. (%) by Alcohol Use During Pregnancy: Drinkers (n=38)	Nondrinkers (n=80)	P (OR)
PIH	9 (24)	9 (11)	<.14 (2.4)
Syphilis	6 (16)	0	<.001
Attempted suicide	2 (5)	0	NS
Chorioamnionitis	2 (5)	0	NS
Genital herpes	2 (5)	0	NS
Gonorrhea	2 (5)	0	NS
Hepatitis	2 (5)	0	NS
Pyelonephritis	2 (5)	4 (5)	NS
Cytomegalovirus	1 (3)	0	NS
Chlamydia	0	2 (3)	NS

*PIH indicates pregnancy-induced hypertension; OR, odds ratio; and NS, not significant.

Table 4.—Condition of Infants at Birth

Maternal Drinking Status, Drinks per Day	No. (%) by Newborn Status*: Liveborn	Fetal Demise/ Neonatal Death	FAS	FAE	Total
Nondrinker	77 (95)†	4 (5)†	0	0	81 (100)‡
4-5	21 (91)†	2 (9)†	0	8 (35)	23 (100)‡
6-7	8 (80)†	2 (20)†	2 (20)	2 (20)	10 (100)‡
>8	5 (71)	2 (29)	4 (57)	1 (14)	7 (100)
Total	**111**	**10**	**6**	**11**	**121§**

*Percentages were computed based on the total number of births within a drinking status category. Fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE) are mutually exclusive categories. Neither FAS nor FAE was diagnosed in any infant in the present study, and the above classification is based on characteristics recorded in the medical records. Alive vs dead neonatally between drinkers and nondrinkers: $\chi^2=2.3$, $P<.13$, odds ratio=3.4.

†Includes one twin.

‡Includes a set of twins.

§Total is total of columns 2 and 3 only.

ence) of infants born to alcohol abusers was significantly below values for infants of nondrinkers ($P<.01$). The birth weight of our control group was at the 25th percentile for national standards, possibly reflecting the generally poor health and nutritional circumstances of the patient population. The differences in birth weight and length were not significant, however, when EGA was held constant with the use of ANCOVA (Table 5). In contrast, head circumference remained significantly smaller ($P<.001$) with EGA held constant with the use of ANCOVA. The twins were apparently not the cause of the lowered birth weight and decreased head circumference among alcohol-exposed infants because the means for these parameters decreased when twins were excluded from the analysis. One-minute, but not 5-minute, Apgar scores were significantly lower in the alcohol-exposed group ($P<.01$) (Table 5).

Table 5.—Infant Characteristics at Birth

	Alcohol Use During Pregnancy						
	Drinkers			Nondrinkers			
Characteristics	n*	Mean	SD	n†	Mean	SD	P
Gestational age, wk	39	36.9	4.1	80	38.7	3.4	<.05
Birth weight, g	40	2554.5	845.8	80	3094.1	640.1	<.01
Birth length, cm	32	46.8	5.0	80	50.1	2.3	<.002
Head circumference, cm	30‡	32.1	3.0	80	34.5	1.1	<.001§
Apgar score							
1 min	36	6.9	2.0	80	8.2	1.9	<.01
5 min	36	8.5	2.1	80	8.7	1.7	NS

*Includes two sets of twins.

†Includes twin A of a twin pair; twin B died and birth characteristics were not available.

‡Excludes one anencephalic infant.

§Analysis of covariance with estimated gestational age as the covariate makes all differences not significant (NS) ($P>.05$) except for head circumference ($P<.001$).

Table 6.—Physical Abnormalities Detected at Birth in 40 Infants Born to Alcohol Abusers and 80* Infants Born to Nondrinkers†

	No. (%) by Alcohol Use During Pregnancy		
Disorder	Drinkers	Nondrinkers	P (OR)
FGR (medical record)	18 (45)	5 (6)	<.001 (16.9)
FGR (≤10th percentile)	11 (28)‡	5 (6)	<.001 (7.2)
Altered palmar creases	5 (13)	0	<.002
Microcephaly (medical record)	3 (8)	0	<.004
Microcephaly (≤10th percentile)	10 (25)‡	0	<.001
Flattened nasal bridge§	3 (8)	0	<.04
Short nose§	2 (5)	0	NS
VSD‖	2 (5)	0	NS
Hypotonia	2 (5)	1 (1)	<.04 (4.9)
Anencephaly¶	1 (3)	0	NS
Coarctation of aorta‖	1 (3)	0	NS
Eyelid ptosis§	1 (3)	0	NS
Hydrocele‖	1 (3)	0	NS
Hydroureter‖	1 (3)	0	NS
Low-set ears	1 (3)	0	NS
Micrognathia§	1 (3)	0	NS
Microphthalmia§	1 (3)	0	NS
Short neck¶	1 (3)	0	NS
Spina bifida¶	1 (3)	0	NS
Facies	6 (15)	0	<.001
Major congenital anomalies	6 (15)	1 (1)	<.009 (13.9)
Neural tube defects	3 (8)	0	<.04
Cardiac defects	3 (8)	0	<.04

*Excludes one twin who died and was unavailable for examination.

†FGR indicates fetal (intrauterine) growth retardation; VSD, ventricular septal defect; OR, odds ratio; and NS, not significant.

‡Contains two twins (not siblings).

§Facial abnormality.

‖Major congenital anomaly.

¶Neural tube defect.

Four infants (1 of whom had a congenital cytomegalovirus [CMV] infection) had the primary features of FAS (facies, microcephaly, FGR, and a major congenital anomaly) noted in their medical records, and 2 additional infants had several primary features associated with FAS (facies, microcephaly, and FGR). Facies (abnormal facial features) are typically difficult to identify; those listed in Table 6 are transcribed exactly as they were recorded in the medical records. The frequencies of diagnosed FGR and FGR less than or equal to the 10th percentile were significantly higher (OR = 16.9, $P<.001$ and OR = 7.2, $P<.001$, respectively) in infants exposed to alcohol in utero (Table 6). The frequencies of major congenital anomalies, congenital cardiac anomalies, and neural tube defects were significantly increased among infants born to alcohol abusers. Of 18 infants reported to have FGR in the medical records, 11 had birth weights below the 10th percentile. A diagnosis of FAS or FAE was *not* recorded in the medical records of any of the infants in this study, although FAE was suggested by FGR in 11 (28%) of 34 liveborn infants of alcoholics, while only 5 control infants (6%) had FGR. Microcephaly was diagnosed in 3 infants, and 10 had head circumferences less than or equal to the 10th percentile (Table 6). These data indicate an FAS prevalence of 1 per 1000 (or 6 per 5602) livebirths for FAS and 2 per 1000 (or 11 per 5602) livebirths for FAE. Thus, total fetal damage due to maternal alcohol abuse was approximately 3 per 1000 (or 17 of 5602) in our study population.

Significantly more infants born to mothers who abused alcohol suffered from perinatal complications in general ($P<.001$, OR = 15.1) (Table 7), although the frequencies of individual complications were not significantly increased. All adverse effects in the alcohol-exposed infants cannot be attributed to alcohol alone because the pregnancies of women who abused alcohol also were more frequently complicated by syphilis as well as tobacco and other drug abuse.

Postnatal follow-up of medical records was available for 22 (65%) of 34 liveborn infants whose mothers abused alcohol during pregnancy; 6 (15%) of 40 infants died during the neonatal period. Eighteen (53%) of 34 infants were receiving care in state hospitals, which is a crude indicator of mental retardation (Table 8). Growth status at or below the 10th percentile was significantly more frequent among alcohol-exposed infants compared with controls (Table 9), indicating postnatal growth retardation, consistent with findings in a previous study.[10]

Table 7.—Perinatal Complications in 40 Alcohol-Exposed Infants Compared With 80 Control Infants*

Complication	No. (%) by Alcohol Abuse During Pregnancy Drinkers	Nondrinkers	P (OR)
Meconium staining	11 (28)	11 (14)	<.21 (2.3)
Hyperbilirubinemia	4 (10)	5 (6)	<.97 (1.5)
Congenital syphilis	3 (8)	0	NS
Irritable and jittery	3 (8)	0	NS
RDS	3 (8)	0	NS
Jaundice	2 (5)	0	NS
Intracranial hemorrhage	2 (5)	0	NS
Meconium aspiration	2 (5)	0	NS
Congenital chlamydia	0	2 (3)	NS
Congenital CMV	1 (3)	0	NS
Cord prolapse	1 (3)	0	NS
Knotted cord	1 (3)	0	NS
Nuchal cord	0	1 (2)	NS
Total	**33** (97)	17 (2)	<.001 (122.3)

*RDS indicates respiratory distress syndrome; CMV, cytomegalovirus; OR, odds ratio; and NS, not significant.

Table 8.—Follow-up of 34 Liveborn Infants at 2 to 10 Years Old

Maternal Drinking Status, Drinks per Day	No. (%) Total Livebirths	Childhood Deaths*	Adoption†	Mental Retardation Institutionalized†	Unknown†
4-5	21 (62)	1 (4.8)	1 (4.8)	8 (38.1)	11 (52.4)
6-7	8 (24)	1 (12.5)	0	6 (75.0)	1 (12.5)
>8	5 (15)	1 (20.0)	0	4 (80.0)	0
Total	**34 (100)**	**3** (9)	**1** (3)	**18** (52.9)	**12** (35)

*Childhood death occurring after the first 28 days of life.
†Percentages were based on the number of livebirths within a drinking category.

Table 9.—Postnatal Growth of 22 Infants Exposed to Alcohol In Utero*

Growth	Alcohol-Exposed	Control	OR	P
Follow-up	22/30 (73.3)	19/80 (23.8)	8.8	<.01
Weight ≤10th percentile	17/22 (77.3)	4/19 (21)	12.8	<.01
Height ≤10th percentile	18/22 (81.8)	5/19 (26.3)	12.6	<.01

*Values are number/total number (percent). The mean (SD) age at follow-up was 4.5 (2.0) years for the alcohol-exposed group and 4.1 (2.9) years for the control group (not significant). OR indicates odds ratio.

COMMENT

In this study, although physical features consistent with FAS were described in the medical records of children born to women who abused alcohol during pregnancy, there was a 100% failure by hospital staff to diagnose the syndrome in our sample. Mental retardation, physical growth delays, and typical facies (short palpebral fissures and hypoplastic mid-face, including a short nose, broad nasal bridge, hypoplastic to absent philtrum, and thin upper lip vermilion) are associated with the FAS. Spinal defects (short neck and spina bifida) and congenital heart disease (atrial septal defect, ventricular septal defect, great vessel defects, and tetralogy of Fallot) are also common among infants with FAS.[2] In one study,[11] children born to women who abused alcohol during pregnancy were found to have physical growth delays of 2 years or more; none of these children were mentally normal, and more than 75% were reportedly profoundly retarded. Other adverse pregnancy outcomes related to alcohol consumption have been reported in the literature, including stillbirths, premature deliveries, growth retardation, and decreased placental weight. Such outcomes may occur even at low levels of alcohol consumption.[10,12-15]

No clear dose-response relationship has been demonstrated between maternal alcohol intake and FAS.[10] However, FAS is usually associated with a maternal intake of 56 to 84 g or more of absolute alcohol per day (equivalent to four to six beers, four to six glasses of wine, or four to six mixed drinks).[1] Actual amounts of alcohol (eg, grams per kilogram per day) and the patterns of consumption (eg, binge drinking vs chronic drinking) associated with FAE, FAS, and reduced size at birth are not known. It is also unclear whether a "safe" level of alcohol consumption during pregnancy exists.[1,6,16-18] Children born of women who drink two to three beers, glasses of wine, or mixed drinks per day during pregnancy may have an increased frequency of FAE that include mild mental retardation, physical growth delays, and behavioral abnormalities, such as hyperactivity. Congenital anomalies that affect an infant's mental and physical development do occur at even low levels of chronic alcohol use during pregnancy.[2] In the present report, poorer outcome was more frequent among infants whose mothers drank more heavily, suggesting a dose-response relationship.

Fetal alcohol syndrome is thought to occur in 30% to 50% of the offspring of alcoholic women (ie, women with a daily intake of eight or more alcoholic beverages).[1,2,11,16,19,20] When infants who do not have all the characteristics of FAS are included, an estimated 50% to 70% of offspring of mothers who drink alcohol daily during pregnancy are probably at risk.[1,11,21,22] Considering the definition of alcoholic consumption in the present study, a prevalence rate for FAS of 80% (4/5) in the offspring of frankly alcoholic women (those who consume eight or more drinks per day) is observed. Two of 6 offspring of women who drank six to seven drinks per day during pregnancy had features consistent with FAS, a rate of 33%.

Fetal alcohol syndrome prevalence varies widely among countries and is estimated at 1 per 100 livebirths in northern France,[23] 1 per 600 in Sweden,[20] and 1 per 750 in Seattle, Wash.[24] In the United States in general, FAS is generally estimated to occur in 1 to 3 per 1000 livebirths[6] and averages 1.9 per 1000 livebirths worldwide.[25] These estimates compared favorably with the estimated FAS prevalence of about 1 per 1000 livebirths seen in our study. Such estimates suggest that FAS is the third most frequent cause of mental retardation, after Down syndrome and neural tube defects.[13,16] Fetal alcohol effects were observed to occur at an estimated rate of approximately 2 per 1000, similar to other estimates.

In this study, it is significant that (1) features of FAS were recorded in the medical records of infants whose mothers drank excessively during pregnancy, (2) there was a 100% failure to diagnose the syndrome, and (3) the obstetric (mothers') medical records contained documentation of maternal alcohol abuse during pregnancy. The ability of physicians who examined these infants to recognize and document some of the less obvious dysmorphic features that may be associated with alcohol abuse during pregnancy must also be questioned due to their failure to diagnose FAS. Therefore, in our study population, there may have been an underestimate of the prevalence of FAS and, even more likely, an underestimate of the number of patients with FAE. Moreover, half or more of the alcohol-exposed infants (17 of 34 and 18 of 34) have had a poor postnatal outcome (delayed physical growth and mental retardation, respectively). Other than presenting information abstracted from medical records, additional statistical comparisons of postnatal follow-up cannot be made because (1) the funds were not available to conduct follow-up of control infants and (2) the follow-up of alcohol-exposed infants was incomplete. Any comparisons made using this incomplete follow-up information could be strongly biased because sick children are more likely to receive medical care and establish medical records than are well infants. Nonetheless, postnatal growth and development of a large proportion of infants born to alcohol abusers is poor.

These findings highlight the need for better communication between obstetric and pediatric staff at the study hospital to establish the diagnosis of FAS or FAE and to provide appropriate medical follow-up for these infants. The establishment of a systemized and collaborative surveillance of women at risk of having a newborn with manifestations of the FAS integrating both pediatric and obstetric services is the most effective means for providing such interspecialty communication.

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Gerald Niedzwiecki (*Contributor*);
Beverly P. Wood, MD (*Contributor and Section Editor*)

A 2½-year-old white male born at term was healthy until 3 weeks of age when his mother reported that his airway seemed congested. He had numerous episodes of pneumonia diagnosed by physical examination and requiring hospitalization at 5 weeks, 7 weeks, 9 weeks, and 4 months of age. During these episodes the patient was afebrile with peaceful tachypnea, upper airway congestion, and intercostal retractions observed. No rales, rhonchi, or wheezes were reported on auscultation of the chest.

Sweat test and upper gastrointestinal series results were negative.

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[redacted]

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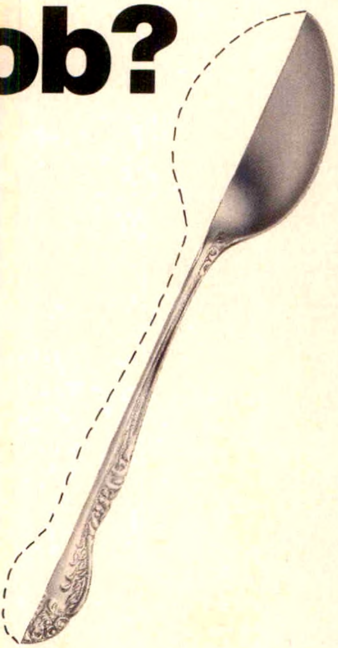

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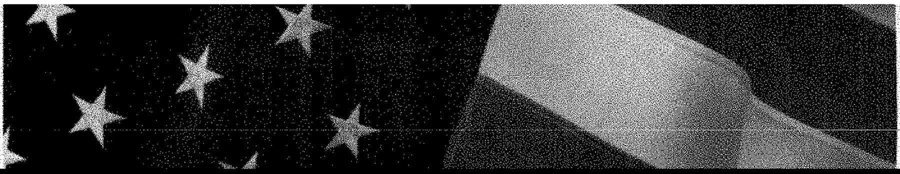

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Current Recommendations for Breast-feeding in Cystic Fibrosis Centers

Elisabeth Luder, PhD; Meyer Kattan, MD; Gail Tanzer-Torres, MS; Richard J. Bonforte, MD

• In recent years, breast-feeding has been strongly recommended, and the decision to breast-feed is made by a large percentage of women before pregnancy. We performed a survey to determine the current recommendations given to mothers in cystic fibrosis (CF) centers. For mothers of infants with CF, 77% of centers recommend breast-feeding alone or with pancreatic enzyme supplements and/or hydrolyzed formula. For mothers with CF, the following responses were given: 11% recommend breast-feeding, 8% do not recommend it, 42% make the recommendation according to the health status of the mother, and 32% make the recommendation according to the personal wishes of the mother. The duration of breast-feeding for mothers of infants with CF was reported to be from 3 to 6 months by 43% of centers, whereas for mothers with CF, 41% of centers reported the duration to be less than 3 months. Several centers reported that their experiences were not always positive, thus indicating a need to establish criteria to predict and ensure a successful outcome.

(*AJDC.* 1990;144:1153-1156)

During this decade, the American Academy of Pediatrics has strongly encouraged breast-feeding.[1] The number of breast-fed infants has grown in recent years among all segments of the general population, and a large percentage of women make the decision to breast-feed before pregnancy.[2] Likewise, mothers of infants with cystic fibrosis (CFIMs) and mothers with cystic fibrosis (MCFs) may decide to breast-feed when given the option to do so. As a result of the potential growth of this phenomenon, it is important to examine current breast-feeding recommendations for the population with cystic fibrosis (CF).

Although successful breast-feeding by MCFs has been reported,[3-8] definitive recommendations cannot be derived from such reports because of small sample size and lack of follow-up. Furthermore, most studies have focused on the nutrient composition of the milk of MCFs rather than the physiologic effects of breast-feeding on the MCF and her infant.

Past investigations of breast-feeding by CFIMs have been limited to retrospective studies and case histories of infants with CF and pancreatic insufficiency who had not received pancreatic enzyme supplements during the time they had been breast-fed.[9,10] Consequently, the results of these studies demonstrated adverse effects resulting from breast-feeding, such as hypoproteinemia and edema due to malabsorption. Although Fleisher et al[11] observed resolution of these conditions when pancreatic enzyme supplements were given with breast milk, they still concluded that infants with CF should not be breast-fed. Likewise, the guidelines for diagnosis and management of CF[12] exclude breast-feeding as a dietary recommendation for small infants. In contrast, more recent recommendations by Dodge[13] and diSant'Agnese[14] include the use of breast-feeding along with pancreatic enzyme supplements if needed. As yet, no studies have been performed to compare the effectiveness of human milk vs formulas or cow's milk in improving the nutritional status of infants with CF.

Because of the lack of information in the literature concerning breast-feeding recommendations in CF, a survey was conducted to examine the breast-feeding recommendations given to patients by CF center directors in the United States. Because most patients who are diagnosed with CF are referred to CF centers, center directors have access to the majority of patients with CF in the United States. It was conjectured that investigation of practitioners' experiences, knowledge, observations, and philosophies may provide insight into breast-feeding practices, as well as reveal whether a consensus exists for recommendations essential to the development of breast-feeding guidelines.

MATERIALS AND METHODS

Methods

In December 1988, a questionnaire was sent to the 124 CF center directors listed in the United States CF Foundation Directory, along with a letter describing the purpose of our research. The questionnaire used closed- and open-ended questions, and an "others" category was provided after each section, with space allocated for additional comments. Questionnaires received by May 1989 were included in this analysis.

Analysis

Because many respondents selected more than one answer for a given question, the response rate for each answer was calculated as a percentage of total responses rather than as a percentage of total centers.

If a center chose the others category exclusive of the choices listed in the questionnaire, then the answer was calculated as part of the response rate for the others category. If, however, a center chose the others category in addition to choosing one or more of the choices listed, then only the answers for the choices listed were considered as part of the overall response rate. This distinction in the calculation of response rates for the others category helps clarify the degree to which a consensus exists for certain answers. Many responses for the others category were com-

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From the Jack and Lucy Clark Department of Pediatrics, Mount Sinai School of Medicine, New York, NY.

Reprint requests to Jack and Lucy Clark Department of Pediatrics, Mount Sinai School of Medicine, One Gustave L. Levy Pl, New York, NY 10029-6574 (Dr Luder).

ments or observations rather than recommendations and thus were not considered as part of the overall response rate.

RESULTS

Of 124 questionnaires, 86 (69%) were completed and returned after two mailings. Responses from centers were equally distributed among all regions of the United States, including Hawaii and

than one of the choices listed.

Protein-energy malnutrition (51.1%) and marked steatorrhea (21.5%) were the most frequently chosen responses to preclude breast-feeding for infants with CF (Table 2). Thirty-seven centers (43%) marked more than one answer. However, 2 centers suggested that in the presence of protein-energy malnutrition, one should first supplement hu-

propriate age to introduce solid foods depends on the infant's weight gain (n = 7); introduce solid foods earlier than planned if the infant has poor weight gain or gastroesophageal reflux (n = 4). Two centers stressed the importance of giving pancreatic enzyme supplements with food as soon as possible, and of providing extra salt to infants with CF, especially in hot weather.

[redacted]

Table 1.—Recommendations About Breast-feeding by CF Center Directors*

Recommendations	Response, No. (%)
For CFIM	
Breast-feeding	
Only	3 (2.6)
Plus pancreatic enzymes	39 (34.2)

Table 2.—Factors for Preclusion or Discontinuation of Breast-feeding According to CF Center Directors*

	Response, No. (%)
Factors for Preclusion	
For MCF	
Inadequate prepregnancy weight	54 (25.5)
Inadequate weight gain during pregnancy	57 (26.9)

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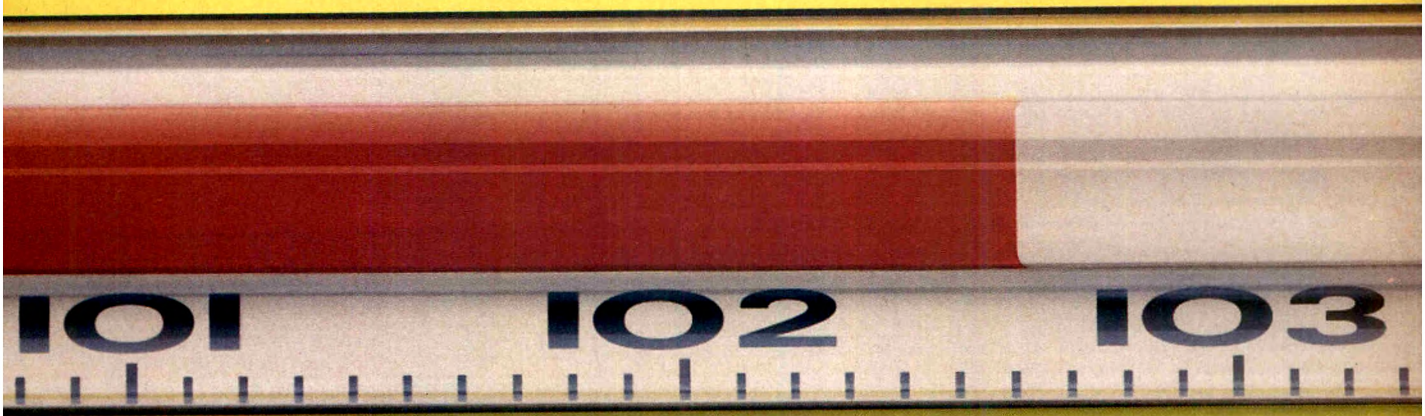

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Anthropometric Parameters of Schoolchildren With Different Life-styles

Joan Sabaté, MD, DrPH; Kristian D. Lindsted, PhD; Ralph D. Harris, MB ChB, FAAP; Patricia K. Johnston, DrPH, MS, RD

• **Height and weight data obtained from a 2-year longitudinal survey were analyzed for 2272 children aged 6 through 18 years who were attending public schools or Seventh-Day Adventist (SDA) schools in southern California. The SDAs do not use alcohol or tobacco, and many adhere to a lacto-ovovegetarian diet. For both sexes, in each school group, the mean height and weight were at or above national reference values. Age-adjusted regression analysis showed that SDA schoolboys were 1.6 cm taller than public schoolboys. There were no significant differences in height for girls. After controlling for height, boys and girls in the SDA schools were found to be leaner than their public school peers, ie, 1.27 and 1.16 kg, respectively. These results suggest that a health-oriented life-style in childhood and adolescence, such as the one followed by SDAs, is compatible with adequate growth and associated with a lower weight for height.**

(*AJDC.* 1990;144:1159-1163)

There is a growing interest in the relationship of life-styles of childhood to atherosclerotic disease prevention in adult life.[1-3] However, there is no clear consensus in the scientific community as to what life-style measures should be followed in early life to prevent adult atherosclerosis.[4,5] Furthermore, concerns have recently been expressed regarding the ability of "prudent" life-styles to support normal growth in children.[6,7] Although experimental studies to evaluate the benefits and risks of a prudent life-style in children are needed, they are not easy to carry out given the ethical concerns and the long time involved. Seventh-Day Adventist (SDA) populations provide a unique opportunity to study the effects of a health-oriented life-style during childhood and adolescence on height, weight, and growth parameters.

The SDAs are members of a conservative Christian denomination with about 700 000 members in the United States.[8] The number of SDA children is estimated at 200 000 in this country. The SDAs follow a health-oriented life-style.[9,10] More than 98% neither smoke nor drink alcoholic beverages, and many follow a lacto-ovovegetarian diet. Nearly all SDAs abstain from the use of pork and tend to avoid caffeine-containing beverages.

Adults SDAs have been studied extensively in relation to health and disease for more than 30 years, and more than 150 reports have appeared in the literature. A substantial lower risk for coronary heart disease compared with non-SDAs has been noted for this population.[9-13] A lower risk for cancer of many sites[14-16] and other prevalent diseases,[17,18] as well as an increased life expectancy, have also been reported.[18-20]

The substantial data on adult SDAs contrast with the paucity of reports that deal with the health status of SDA children. Most of the few studies of SDA youngsters have been limited to a description of dental caries prevalence[21-23] and cardiovascular disease risk factors.[24-26] Limited information is available on the body size of SDA preschoolers[27] and adolescents[26,28] who follow a vegetarian diet; however, to our knowledge, no data have been published on the physical growth and size of school-age SDA children. This study compares the anthropometric parameters of children who were attending SDA parochial schools with those in public schools, all of whom participated in the Child-Adolescent Blood Pressure Study in southern California.[24]

SUBJECTS AND METHODS

The study design and data collection procedures for the several phases of this study have been described in detail elsewhere.[24] In brief, during phase 1, children from the first through 10th grades were screened from 16 SDA parochial schools and 13 public schools in the Los Angeles, Calif basin. Informed consent from the parents was obtained before data collection. Height, weight, blood pressure, and demographic data were documented for 7840 children aged 6 through 17 years, or 84% of the eligible students. Refusal rates were low, less than 2%. The major limiting factor in obtaining data was absence from school on days that the field team collected data (14%). Phase 2 data collection was carried out a year later and limited to non-Hispanic white children. Height and weight measurements were taken from 1090 SDA and 1182 public school children who had been randomly sampled from the upper, intermediate, and lower levels of the phase 1 blood pressure distributions for each age, sex, and school group. The distribution of these children is shown in Table 1. Dietary information was obtained for a subsample of 870 SDA and 895 public school children. In phase 3, demographic, life-style, and anthropometric data were collected for the parents of about a 50% subsample of phase 2 children.[24]

To characterize the dietary habits of the children studied, a 106-item food frequency questionnaire was developed and validated. The questionnaire was self-administered by all youngsters aged 10 years or older and completed by the mothers of children aged 6 to 9 years. For each child, we constructed a simple frequency index that gave an approximate monthly consumption of foods for each of six food groups (Table 2) as follows: (1) meat—including poultry and fish; (2) dairy products—milk, cheese, ice cream, yogurt, and eggs; (3) fruit and vegetables—both fresh and canned; (4) starchy foods—breads, cereals, pasta, and legumes; (5) "junk foods"—candy, cookies, potato chips, and other snack foods; and (6) vegetable protein products.

Height was recorded by using a portable stadiometer, with the child standing erect in

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From the Departments of Epidemiology (Drs Sabaté and Lindsted) and Nutrition (Dr Johnston), School of Public Health, and the Department of Pediatrics, School of Medicine (Dr Harris), Loma Linda (Calif) University.

Reprint requests to Department of Epidemiology, School of Public Health, Loma Linda (Calif) University, Loma Linda, CA 92350 (Dr Sabaté).

Table 1.—Age-Specific Mean Heights, Weights, and BMI of Boys and Girls Attending SDA and Public Schools*

		Height, cm						Weight, kg				BMI			
		SDA Schools			Public Schools			SDA Schools		Public Schools		SDA Schools		Public Schools	
	Age, y	n	Mean	SD	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Boys	6.5-7.5	4	128.9	4.0	14	124.5	6.2	26.1	1.5	24.9	3.6	15.7	1.1	16.0	1.0
	7.5-8.5	42	128.9	5.4	57	127.1	5.6	27.0	5.0	26.0	4.0	16.6	1.9	16.0	1.6
	8.5-9.5	49	135.3	6.8	53	133.9	6.5	31.2	5.5	30.1	4.5	16.9	1.8	16.7	1.6
	9.5-10.5	58	140.4	5.8	79	138.8	5.7	33.0	4.7	33.0	6.6	16.7	1.5	17.0	2.6
	10.5-11.5	58	144.0	5.7	43	145.3	6.9	36.1	6.6	39.0	7.6	17.3	2.3	18.4	2.6
	11.5-12.5	59	150.8	6.3	55	148.9	7.8	42.1	8.3	41.7	10.0	18.4	2.7	18.6	3.0
	12.5-13.5	70	158.4	7.5	36	157.3	8.4	47.7	9.5	50.3	16.5	18.8	2.6	20.1	5.8
	13.5-14.5	67	165.8	8.6	68	163.6	8.5	54.8	11.2	52.3	9.1	19.9	3.5	19.5	2.6
	14.5-15.5	63	173.7	8.3	56	169.8	9.7	61.1	8.6	59.3	12.8	20.2	1.9	20.4	3.2
	15.5-16.5	44	176.9	8.6	85	175.0	8.0	66.3	13.5	65.1	10.5	21.1	3.2	21.2	2.8
	16.5-17.5	24	177.4	5.8	57	176.9	6.8	66.2	6.5	68.8	9.4	21.0	1.6	21.9	2.5
	17.5-18.5	4	177.8	3.8	6	182.9	6.2	78.0	13.4	73.1	7.1	24.8	5.3	21.9	2.4
Girls	6.5-7.5	3	125.3	5.2	12	122.7	5.6	26.3	1.4	23.3	4.4	16.0	1.1	15.4	2.0
	7.5-8.5	50	129.3	5.9	53	128.1	6.1	27.4	4.8	27.6	5.2	16.3	1.8	16.8	2.4
	8.5-9.5	65	133.7	5.3	61	133.4	5.5	29.5	4.8	31.7	6.0	16.4	1.8	17.7	2.5
	9.5-10.5	61	140.0	7.0	39	139.8	6.6	33.2	5.4	34.7	8.4	16.9	1.8	17.7	3.4
	10.5-11.5	48	146.0	6.3	62	147.7	7.6	36.5	6.0	40.3	9.4	17.0	1.8	18.2	2.8
	11.5-12.5	43	150.3	7.5	52	151.9	8.2	40.9	7.1	42.0	9.3	18.0	2.1	18.0	2.5
	12.5-13.5	54	158.7	5.8	34	158.8	7.9	50.0	8.7	50.9	12.4	19.8	2.8	20.0	3.8
	13.5-14.5	83	163.5	6.2	67	162.3	5.7	55.1	11.4	51.6	8.9	20.6	3.9	19.6	2.9
	14.5-15.5	79	164.0	5.7	61	164.3	7.0	54.3	7.9	56.0	9.9	20.2	2.4	20.7	3.1
	15.5-16.5	43	164.2	5.8	89	164.7	6.2	55.2	7.2	58.4	11.0	20.5	2.3	21.6	4.0
	16.5-17.5	16	163.2	6.3	41	163.9	5.2	56.4	6.6	57.5	11.3	21.2	2.6	21.4	4.0
	17.5-18.5	3	165.7	4.5	2	168.3	2.6	56.1	4.5	60.3	5.1	20.4	1.5	21.3	1.1

*BMI indicates body mass index (weight [kilograms]/height [squared meters]); SDA, Seventh-Day Adventist.

stocking feet without upward pressure exerted on the mastoids. Weight was recorded, with the child wearing light clothing without shoes, by using a portable beam scale. Two observers recorded the anthropometric measurements. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Height velocity (growth rate) was expressed in centimeters per year; it was computed by dividing the difference in height between phase 2 and phase 1 data collection by the time between measurements. Height velocity was plotted against age at the last measurement. Age was computed by subtracting the birth date from the last data collection date. Age was used as a continuous variable for all analyses; however, it was categorized for constructing tables.

To test for significant differences in attained height, weight, and BMI among the school subgroups, we performed sex-specific, age-adjusted multiple linear regression analyses.[29] Since height, weight, or BMI might not be related linearly with age, we first determined the best-fitting model between height, weight, or BMI and age. Selection criteria for the best model was the highest coefficient of determination (R^2) with minimal colinearity. Age and age-cubed were included in the final model for height, and age alone was included on the models for weight and BMI. We tested for school differences by including a binary variable for school group.

Since weight is related to height, it was necessary to control for height when studying differences in weight between the two school systems. We used two approaches: (1) testing for differences in Quetelet's index, and (2) controlling for height when testing for weight differences.

RESULTS

Table 2 shows the mean consumption (times per month) of the six food groups according to the school system, indicating the 25th and 75th percentiles. The SDA schoolchildren ate meat, dairy products, eggs, and junk food less frequently, and they ate fruits, vegetables, starchy foods, and vegetable protein products more frequently than public school children.

Table 1 shows the mean height, weight, and BMI by age, sex, and school groups. The samples were normally distributed, but were considered too small to show percentiles. Except for the extremes of the age distribution, where subjects were few, there were about 50 subjects in each age-sex-school group.

For both sexes in each school group, the mean height values were well above the 50th percentile of the National Center for Health Statistics reference values,[30] except for 12-year-old SDA girls, who were 1.2 cm below, at approximately the 45th percentile.

The SDA school boys were taller than public school boys throughout the age range studied, except at 11 and 18 years. The latter age category, however, contained only a few subjects. Age-adjusted regression analysis revealed that SDA school boys were 1.6 cm taller

Table 2.—Frequency of Use (Times per Month) of Six Food Groups by SDA and Public Schoolchildren in Southern California*

	Mean ± SD (Interquartile Range, 25th-75th Percentiles)		
	SDA Schools (n = 870)	Public Schools (n = 895)	P†
Meat group	27.8 ± 39.7 (0-38)	86.4 ± 56.0 (52-104)	<.001
Dairy products and eggs	84.6 ± 37.4 (60-102)	92.4 ± 43.4 (64-108)	<.001
Fruit and vegetables	120.9 ± 63.2 (72-160)	94.5 ± 58.9 (52-124)	<.001
Starchy foods	84.2 ± 39.6 (58-102)	77.8 ± 45.5 (47-98)	.002
Junk foods	67.0 ± 46.3 (36-86)	95.6 ± 62.5 (53-114)	<.001
Vegetable protein products‡	32.9 ± 33.2 (12-44)	...	...

*SDA indicates Seventh-Day Adventist.
†*P* value of the *t* test comparing the frequency of use among children of both school systems.
‡Vegetable protein products were not included in the questionnaire given to public schoolchildren.

Table 3.—Multiple Linear Regression Coefficients for Various Predictors of Height and Weight in 2272 School-age Children in Southern California

	Boys (n = 1151)			Girls (n = 1121)		
Term	Estimated Effect	SE	*P*	Estimated Effect	SE	*P*
		Height				
Age, y	6.71 cm	0.39	<.001	10.30 cm	0.35	<.001
Age cubed, y^3	0.002 cm	0.00	.030	−0.01 cm	0.00	<.001
SDAs vs public*	1.56 cm	0.44	<.001	−0.01 cm	0.38	.970
Constant	73.76 cm	3.07	<.001	49.92 cm	2.76	<.001
		Weight				
Age, y	0.357 kg	0.182	.050	0.788 kg	0.158	<.001
Height, cm	0.776 kg	0.028	<.001	0.674 kg	0.030	<.001
SDAs vs public*	−1.276 kg	0.421	.002	−1.163 kg	0.432	.007
Constant	−77.134 kg	2.46	<.001	−66.812 kg	3.02	<.001

*Seventh-Day Adventists (SDAs) compared with public schoolchildren.

($P<.001$) than public school boys (Table 3). No significant differences existed between school types for girls.

Analyses on a subsample of 478 boys and 495 girls for which the height of their biological mother and/or father was measured (phase 3 of the study) showed similar results. The SDA school boys were 1.3 cm taller ($P<.05$) than public school boys, and no significant height differences existed for girls. Further control for socioeconomic factors, such as family income, parents' education, or father's occupation, did not change the results. (When parental heights were in the regression model, socioeconomic factors had no independent statistical significance.)

The mean weight for each age-sex-school group was at or above the National Center for Health Statistics reference values,[30] except for 12-year-old SDA school girls who were also slightly shorter and SDA school girls aged 15 ½ to 18 ½ years who were below reference values. The SDA school girls tended to weigh less than public school girls, but the differences did not reach statistical significance in univariate analysis. No significant differences in weight existed between the boys.

The BMI for girls who were attending SDA schools was 0.433 lower ($P=.01$) than their counterparts in public schools. The SDA school boys showed a nonsignificant tendency for a lower BMI (data not shown). The SDA school boys and school girls were significantly lighter (1.276 and 1.163 kg, respectively) than their counterparts at public schools, when weight was compared after controlling for height differences (Table 3).

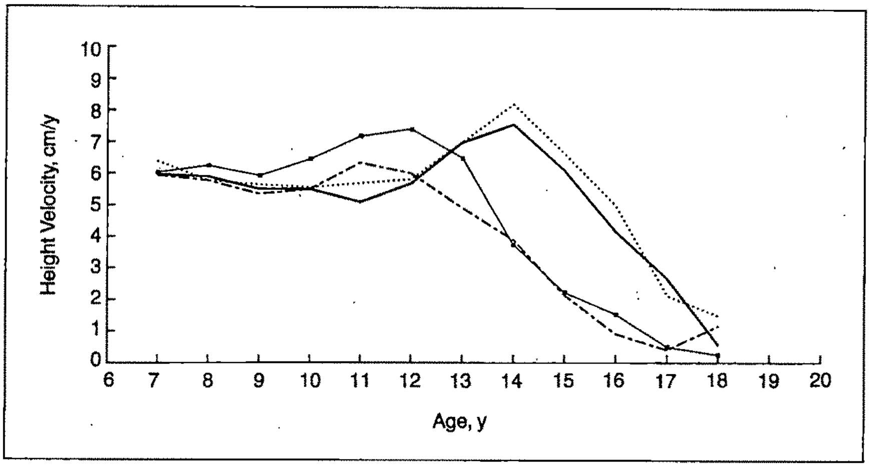
The mean height velocities for each group are graphically presented in the Figure. The height velocity decreased and was similar in all groups during the preadolescent years. Onset of the pubertal growth spurt occurred at age 9 years in public school girls, at age 10 years in SDA school girls, and near age 12 years for boys in both school systems. Age at the peak increment was at 11 years for girls and 14 years for boys of both school systems. The magnitude of the growth spurt was greater in public school children than in SDA schoolchildren; it was also greater for boys than girls in both school groups.

COMMENT

The dietary patterns of children who were attending SDA schools were similar to the ones previously reported in the adult SDA population.[9,10] A striking difference between the two school systems was the lower frequency of meat consumption by SDA school children (Table 2). It is reasonable to assume that the diets of the SDA school children were lower in saturated fat, cholesterol, and possibly total fat since they also ate dairy products, eggs, and junk foods (potato chips and other fried snacks) much less frequently than a comparable group of children who were living in the same geographical area.

We studied children in southern California who were taller and heavier than national standards.[30] The salient findings are that SDA school boys were significantly taller than public school boys of the same age, and that both boys and girls in SDA schools were leaner than their counterparts in the public schools. These differences cannot be attributed to methodology, since data were collected by the same team with the use of the same instruments and protocol in both school systems.

There is no reason to believe that SDAs have a genetic predisposition to be taller or slimmer, any more than they



Growth rate of Seventh-Day Adventist and public school children. Dark solid line indicates Seventh-Day Adventist school boys; dashed line, Seventh-Day Adventist school girls; dotted line, public school boys; and light solid line with squares, public school girls.

have a genetic predisposition to have a lower risk for ischemic heart disease.[31,32] Fathers' and mothers' heights are proxy measures of the genetic influence on height. We do not have these variables for the entire study population, but data available on a subsample of parents who participated in phase 3 of the study (data not presented) showed no significant difference in parents' height for the two school systems. Moreover, testing for height differences on a subsample of children from the two school systems, while controlling for fathers' and mothers' heights, did not substantially change the results that SDA school boys were taller.

California SDAs have previously been shown to be better educated than the general population,[13] and private (SDA) school students may have a higher socioeconomic status than public school students. However, these factors, when considered together with parental height, did not seem to explain the taller stature of SDA school boys in the present study. Although social factors have been positively related to the height of school-age children in many populations,[33] recent studies that have looked concurrently at the influence of social and biological factors have found that the greater proportion of variation in children's height is explained by parental height and not by socioeconomic variables.[34,35]

It is reasonable to suspect that weight and height differences observed between the school groups may be related to the life-style of the children and/or their parents. It is worth mentioning that the comparison was not strictly between SDAs and non-SDAs, since the SDA schools were estimated to have a 10% enrollment of non-SDAs (Office of Education of the SDA Church, written communication, March 6, 1989), and the public schools were estimated to have about 5% of SDAs. If any life-style characteristics were related to physical growth, this degree of dilution would tend to decrease any differences that we found.

The vegetarian diet followed by a large percentage of our SDA study population (Table 2) has been associated with lower weights in both adults and children.[36-42] However, other authors found no difference between the weight of adult vegetarians and nonvegetarians,[23,43,44] and Quetelet's index of SDA adolescents in Illinois was similar to that in the general US population.[26] We did not find significant differences for either sex between school groups when unadjusted weight data were compared. However, when weight differences were tested, controlling for height, SDA school boys and school girls were shown to be significantly leaner. This relatively lower weight for height may result in a health advantage in adult life.

Children who were attending SDA schools were possibly exposed to much less passive smoking in both their intrauterine and extrauterine lives than children who were attending public schools. This may explain some of the height differences between the groups. The negative association of maternal smoking with growth is well known for young children,[45-47] but in older ages, it is less clear as to whether the retarding effect on physical development is due entirely to maternal smoking during pregnancy or passive smoking during childhood.[48,49] There is a dose-response relationship with the amount of current maternal smoking and the attained height of children aged 6 to 11 years.[49] Children of nonsmoking mothers were approximately 0.65 cm taller than children of heavy smokers,[49] and in 14-year-old children, the difference was a few millimeters.[50]

It is unclear why differences in height were found in boys but not in girls. Genetic and environmental factors could be expected to have similar effects in both sexes, but it is possible that the later onset of maturation in SDA school girls compared with public school girls obscured the effect of these factors on height. The relatively later onset of the adolescent growth spurt in SDA school girls (Figure) may denote a diet-related delay in physical maturation. A later age at menarche in vegetarian girls has been reported.[51,52] However, the height velocity curves from our 1-year longitudinal study are related to chronological age, which is a poor indicator of development during adolescence.[53] Such curves are not representative of the shape and size of the true velocity curve[54,55]; the magnitude and duration of the true height velocity spurts cannot be ascertained accurately in this study. Other parameters of maturation, such as bone age or secondary sexual characters, were not available in this study.

The role of diet on physical growth in this population will be reported in a forthcoming study; however, longitudinal studies from birth to adulthood that look at the time and rate of maturation concurrently with anthropometric parameters and dietary intake are needed to provide information regarding the relatively unknown interactions of diet, maturation, and growth.

In conclusion, the results of this study suggest that a health-oriented life-style during childhood and adolescence, such as the one followed by many SDAs, sustains adequate physical growth. This life-style is also associated with a lower relative weight of school-age children.

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Cardiovascular Effects of Caffeine Therapy in Preterm Infants

Frans J. Walther, MD, PhD; Rosanna Erickson, RN, NNC; Maureen E. Sims, MD

• Theophylline therapy increases left ventricular output in preterm infants by a combination of positive inotropic and chronotropic effects. The cardiovascular effects of caffeine were evaluated in 20 clinically stable preterm infants. Ten infants received intravenous caffeine citrate with a loading dose of 20 mg/kg and a maintenance dose of 5 mg/kg every 24 hours, and 10 infants were control subjects. Left ventricular output, stroke volume, and heart rate were measured by using a combination of two-dimensional and pulsed Doppler echocardiography and mean arterial blood pressure by oscillometry (Dinamap, Critikon, Division of McNeil Laboratories, Irvine, Calif) before the start and on days 1, 2, 3, and 7 of caffeine therapy and 7 days after discontinuation of therapy. Compared with controls, left ventricular output and stroke volume were significantly increased on days 1 to 7 of caffeine therapy. Caffeine led to an increase in the mean arterial blood pressure on the first 3 days of therapy, but the heart rate did not change. These data indicated that caffeine administration leads to a significant increase in left ventricular output in preterm infants and that this inotropic effect is accompanied by a pressor effect.

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Methylxanthines, specifically theophylline and caffeine, are used frequently in the neonatal intensive care setting. Similar to theophylline, caffeine is used to treat apnea of prematurity[1] and to assist weaning of preterm infants from mechanical ventilation.[2] In a previous study, we reported that theophylline therapy increases left ventricular output in preterm infants by a combination of positive inotropic and chronotropic effects, but lacks a pressor effect.[3] In vitro, caffeine has been shown to exert an inotropic effect on ventricular myocardial fibers.[4] Caffeine research in newborn infants has concentrated on its pharmacokinetics[5] and its effects on respiratory function.[6] We evaluated the effects of caffeine on cardiac function and blood pressure in preterm infants.

SUBJECTS AND METHODS

The study population consisted of 20 preterm infants, of whom 10 were to receive caffeine for apnea of prematurity (n=2) or weaning from the ventilator (n=8), and 10 were matched for age, weight (within 50 g), and ventilator status as controls. All infants were born and treated at the Los Angeles County–University of Southern California Medical Center, Los Angeles, Calif, and their conditions were clinically stable with hematocrit values greater than 0.40, serum calcium levels between 1.87 and 2.49 mmol/L, and mean airway pressures less than 6 cm H_2O. The protocol was approved by the research committee, and informed parental consent was obtained before entry into the study. Exclusion criteria were as follows: infants who were small for gestational age; infants of diabetic mothers; infants with congenital heart disease, patent ductus arteriosus, or left ventricular myocardial dysfunction; and infants with an increasing mean airway pressure before the start of treatment. None of the infants were receiving pressor drugs, digoxin, phenobarbital sodium, phenytoin sodium, or theophylline. All infants were in incubators, with their skin temperatures maintained at 36.0°C to 36.5°C.

Caffeine was administered intravenously during a period of 20 minutes with a loading dose of 20 mg/kg of caffeine citrate (equivalent to 10 mg/kg of caffeine base) and a maintenance dose of 5 mg/kg of caffeine citrate (equivalent to 2.5 mg/kg of caffeine base) every 24 hours. Caffeine serum concentrations were determined by high-pressure liquid chromatography (Smith Kline Bio-Science Laboratories, Van Nuys, Calif)[7] before the start of caffeine therapy, 1 hour before the scheduled administration of maintenance dosages on days 1, 2, 3, and 7, and 7 days after the discontinuation of caffeine therapy. In the controls, serum caffeine levels were drawn following a similar time schedule; the lower limit of detection was 2 mg/L.

Left ventricular output, stroke volume, heart rate, and mean arterial blood pressure were measured 1 hour before the start of caffeine therapy, 1 hour before the scheduled administration of maintenance dosages on days 1, 2, 3, and 7, and 7 days after discontinuation of caffeine therapy. In the controls, echocardiographic examinations were performed by using a similar time schedule. The left ventricular output (in milliliters per minute per kilogram) was estimated from the mean blood flow velocity in the ascending aorta and the internal aortic root diameter was estimated by using a combination of two-dimensional and pulsed Doppler echocardiography (Ultramark 8, Advanced Technology Laboratories, Bothell, Wash).[8] The stroke volume (in milliliters per kilogram) was calculated from the left ventricular output and the heart rate measured from the electrocardiogram. All infants were either sleeping or resting during the procedure. The mean arterial blood pressures were measured in triplicate by oscillometry (Dinamap, Critikon, Division of McNeil Laboratories, Irvine, Calif). The observers were "blinded" as to the treatment group.

Results are expressed as mean ± SD. Statistical analysis was done by an unpaired Student's *t* test and regression analysis.

RESULTS

The 10 infants in the caffeine-treated group had a mean ± SD birth weight of 1308 ± 500 g (range, 640 to 1980 g) and a gestational age of 29.6 ± 3.0 weeks (range, 25 to 33 weeks). The 10 controls had a mean birth weight of 1284 ± 478 g (range, 680 to 1940 g) and a gestational age of 29.6 ± 3.0 weeks (range, 25 to 33 weeks). The median postnatal age was 6 days (range, 2 to 32 days) in both groups. The mean weight at the start of the study was 1306 ± 404 g (range, 790

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From the Neonatology Division, Department of Pediatrics, University of Southern California School of Medicine, Los Angeles County–University of Southern California Medical Center, Los Angeles, Calif. Dr Walther is now with the Department of Pediatrics, King/Drew Medical Center and UCLA School of Medicine.

Reprint requests to Department of Pediatrics, King/Drew Medical Center and UCLA School of Medicine, 12021 S Wilmington Ave, Los Angeles, CA 90059 (Dr Walther).

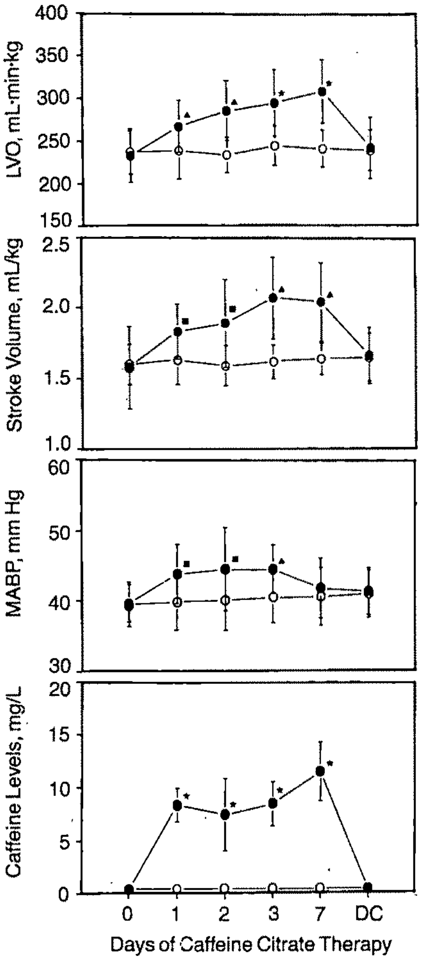
to 1820 g) in the caffeine-treated group, and it was 1291±424 g (range, 780 to 1890 g) in the controls. The weight gain during the study was similar in both groups. At entry into the study, 8 infants in each group were receiving mechanical ventilation (mean airway pressure, 4.2±0.8 cm H_2O; fraction of inspired oxygen, 0.36±0.13). During the study period, 5 infants in the caffeine-treated group and 4 of the controls were extubated. All infants had been studied for at least 3 days before extubation was performed. In the remaining 7 infants, all measurements were taken during mechanical ventilation. Two infants in the caffeine-treated group with apnea and 2 controls never received mechanical ventilation. Six infants in the caffeine-treated group and 5 controls had histories of hemodynamically significant patent ductus arteriosus. All of these infants had been treated with indomethacin and/or ligation, and ductal closure was confirmed before entry into the study.

In the controls, the left ventricular output, stroke volume, mean arterial blood pressure, and heart rate did not vary considerably, although the mean arterial blood pressure tended to increase slowly during the study period (Figure). The infants in the caffeine-treated group showed a significant increase in the left ventricular output and in the stroke volume on days 1, 2, 3, and 7. This was accompanied by a higher mean arterial blood pressure on days 1, 2, and 3 (Figure). The heart rate did not change significantly during caffeine therapy.

The mean caffeine level was 9.44±2.82 mg/L in the caffeine-treated group. Linear regression analysis showed a significant relation between caffeine levels and left ventricular output ($r=.56$, $df=39$, $P=.00035$) and, to a lesser extent, between caffeine levels and stroke volume ($r=.39$, $df=39$, $P=.01595$).

COMMENT

Caffeine seems to have a positive inotropic[9-11] and a pressor effect[12-14] in adults. Explanations for the positive inotropy include an increase in cyclic adenosine monophosphate levels via inhibition of phosphodiesterase, release of calcium from the sarcoplasmic reticulum, and antagonism of endogenous adenosine receptors.[4,9-11] The pressor effect might contribute to hypertension.[12-14] Our study demonstrates that in preterm infants caffeine exerts a positive inotropic effect with a concomitant slight, but significant, increase in blood pressure during the first days of its administration. Whereas positive inotropy persisted during caffeine therapy, blood pressure had returned to baseline values by day 7. The increase in left ventricular output amounted to 20% to 30% and was comparable with that seen following administration of theophylline to preterm infants in a recent study by our group.[3] However, in that study, theophylline therapy had an inotropic and a chronotropic, but not a pressor effect.



Mean±SD values of left ventricular output (LVO), stroke volume, mean arterial blood pressure (MABP), and serum caffeine levels before and during the first 7 days of caffeine therapy and 7 days after its discontinuation (DC). Closed circles indicate caffeine-treated group; open circles, controls; squares, $P<.05$; triangles, $P<.01$; and stars, $P<.001$ vs controls.

Theophylline and caffeine decrease peripheral vascular resistance in adults.[14] This fall in resistance alone could explain the increase in cardiac output and certainly contributes, in combination with augmentation of left ventricular output, to increased blood flow. Although theophylline and caffeine increase systolic blood pressure, only caffeine seems to increase the diastolic blood pressure.[15,16] The latter may explain the increases in the mean arterial blood pressure in our group of preterm infants receiving caffeine therapy. In a recent study on caffeine and cerebral blood flow velocity in seven preterm infants, Saliba et al[17] found an increase in the heart rate, but not in the mean arterial blood pressure during the first 2 hours after an intravenous loading dose of 20 mg/kg of caffeine citrate. This discrepancy with our findings is probably secondary to the differences in the duration and timing of the studies. However, most indirect methods of arterial blood pressure measurement, such as oscillommetry, are fairly reliable in determining the systolic pressure, but less so in determining the diastolic pressure[18]; this may decrease the accuracy of mean arterial blood pressure values obtained this way. Methylxanthines have an effect on fluid balance and may alter the loading conditions of the heart during their administration. However, we have no data regarding central venous pressure or some other estimate of preload to estimate this effect. It is, therefore, unclear that a true pressor effect exists.

Although the changes in blood pressure secondary to caffeine therapy were small, they might potentially contribute to peri-intraventricular hemorrhage in susceptible preterm infants. The augmentation in the left ventricular output may increase oxygen consumption, just like theophylline does. These effects of caffeine therapy must be considered when clinical decisions are made on the type of methylxanthine to be used in a preterm infant.

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Daniel Torphy, MD
Department of Pediatrics
MEDICAL COLLEGE OF WISCONSIN
1700 West Wells Street
Milwaukee, WI 53233

Equal opportunity, affirmative action employer, M/F/H

BC/BE PEDIATRICIAN wanted to join two pediatricians in well-established, growing pediatric practice affiliated with medical center. Beautiful location, family oriented. First year salary with malpractice, health and disability insurance, four weeks vacation, and CME allowance. Early partnership for right physician. Contact: Dr. Feipon, Alvarado & Associates, P.A., 207A Maryland Avenue, Salisbury, MD 21801.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

HERSHEY, PENNSYLVANIA — Rapidly growing solo practice with CRNP seeking two BC/BE pediatricians. Practice has special emphasis on behavioral developmental pedicatrics, allergy/asthma. Two community hospitals with Level III nurseries available. Many life style amenities. Contact: Glen S. Bartlett, MD, Hershey Pediatric Center, 441 East Chocolate Avenue, Hershey, PA 17033. (717) 533-7850.

ROCHESTER, NEW YORK

Eleven-member pediatric division of multispecialty group practice serving prepaid and fee-for-service patients looking for twelfth pediatrician to do both general pediatrics and departmental administration. Previous experience in medical management preferred. Subspecialty interests possible. University affiliation encouraged. Competitive salary and benefits. Located in attractive metropolitan area with many cultural and recreational advantages.

Send resume or call:

ROCHESTER MEDICAL GROUP, P.C.
Attention: James Tobin, MD
800 Carter Street, Rochester, NY 14621
(716) 338-1400, Extension 4040. EOE, M/F

THIRD PEDIATRICIAN — BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105, or (218) 829-4901. Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

ESTABLISHED two person practice experiencing explosive growth looking for BE/BC pediatrician. Located on the beautiful southern California coast, one hour north of Los Angeles. May begin anytime. For information contact: Mark Freedenberg, MD, 2793 Loma Vista Road, Ventura, CA 93003. (805) 656-3900.

PEDIATRICIAN (GENERAL): Suburban Boston staff model HMO, committed to quality personalized care, has an immediate opening for a BE/BC pediatrician. As a full-time member of our respected staff, you will work in our modern, well equipped facility located in the Merrimack Valley area of Massachusetts, just 22 miles north of Boston. We are seeking candidates with impeccable credentials, emphasizing interpersonal skills and a commitment to primary patient care. Competitive salary and benefit package. Send CV to: Director of Professional Human Resources, Medical East Community Health Plan, One Worcester Road, Framingham, MA 01701; or call: (508) 879-0077 collect.

PEDIATRICIAN — Board-certified/-eligible. Excellent opportunity for well-trained physician to join a 50-physician multi-specialty group in progressive, dynamic practice. Well-established, 5-physician department. Affiliate hospital recently underwent complete renovation and expansion. Competitive salary/comprehensive benefit package includes: malpractice insurance, flexible benefits plan, 401K and profit sharing, relocation assistance. Send CV: Olmsted Medical Group, Attention: Susan Schuett, 210 Ninth Street Southeast, Rochester, MN 55904.

WASHINGTON — BC/BE pediatrician to join one pediatrician in busy general pediatric practice at multi-specialty clinic; excellent facilities at both clinic and hospital. Excellent salary and benefits. Prime outdoor recreational area. Contact: Terry Coplin, 840 Hill Avenue, Moses Lake, WA 98837. (509) 765-0216.

INFECTIOUS DISEASE SPECIALISTS

The Saudi Arabian Oil Company's (SAUDI ARAMCO) Dhahran Health Center (DHC) in Saudi Arabia needs **Pediatric Infectious Disease Specialists** to join a staff of 17 in its modern 483-bed hospital.

The DHC functions as a referral center for a patient population of approximately 200,000 and the medical problems encountered are varied and challenging. It has the latest medical equipment and special care units including a 10-bed Neo-Natal ICU, a 8-bed Pediatric ICU, and a 16-bed intermediate care unit.

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Employment with Saudi Aramco will provide you with an interesting lifestyle in a multicultural environment with comfortable family living arrangements. Benefits include free medical care while in Saudi Arabia, fine schools and a broad spectrum of recreational opportunities. We provide an attractive compensation package including an expatriate premium plus 36 calendar days of vacation annually, allowing for extensive travel.

For consideration, **CALL OUR 24 HOUR, 7 DAYS PER WEEK TOLL-FREE NUMBER 1-800-221-3333, EXT. R11.**

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STUDY OF SHORT STATURE

The Developmental Endocrinology Branch of the National Institute of Child Health and Human Development (NICHD) is recruiting children with non-growth hormone-deficient short stature for a placebo-controlled trial of the effect of growth hormone treatment on final adult height.

Children may be 9 to 14 years of age, prepubertal or just-starting puberty, shorter than the median height of children 2-1/2 years younger. Health should be normal. Children with prior growth hormone or androgen treatment, or current ritalin or steroid treatment are not eligible to take part. Children will be evaluated to determine that their growth hormone secretion is normal. Children will be assigned randomly, in a double-blind fashion, to receive either growth hormone or placebo injections three days per week until adult height is achieved.

There is no charge for evaluations performed or for treatment received as part of this study. Patients must be able to visit the NIH campus in Bethesda, Maryland (near Washington, DC) every six months. Travel costs will be provided once patients have been admitted to the study.

Gale Heavner, R.N.
Study Coordinator
(301) 496-8205;

Susan R. Rose, M.D.
University of New Mexico
(505) 277-5551;

Judith Levine Ross, M.D.
Hahnemann University
(215) 448-7710;

Gordon B. Cutler, Jr., M.D.,
Chief, Section on Developmental Endocrinology
Bldg 10, Rm 10N262,
National Institutes of Health
Bethesda, MD 20892
(301) 496-4686

PEDIATRICIAN — Thriving, general pediatric practice, lovely suburban New Jersey location, strong emphasis on patient education and highest quality care seeks BC/BE pediatrician, half- or full-time to start as soon as possible. Salary/benefits negotiable. Partnership option. Send CV/resume to: Box #114, c/o AJDC.

PEDIATRICIAN

Salary above minimum is based on training and experience. Immediate openings for board-eligible pediatrician for Wayne County Health Department Clinic. Full-time, 8:00 AM - 4:30 PM, Monday- Friday. Excellent benefits.

Send resume or CV to:
Wayne County
Health Department
Wayne County Complex
Westland, MI 48185
Attention: Patricia Fleming
(313) 467-3399
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SOUTHERN OHIO: Seventh BE/BC pediatrician for 60 plus physician M/S group in progressive, scenic community. Enjoy top income, partnership in year two, 6 plus weeks vacation/CME, and extensive benefits. 269-bed hospital with approximately 1,200 births adjoins clinic. Call Georgetta: (800) 328-3666.

SOUTH CENTRAL PENNSYLVANIA: Join two, young BC pediatricians in busy practice 1½ hours from DC. Offer includes salary plus production bonus, paid malpractice, health insurance, and potential partnerhsip. Attractions: 217-bed hospital, 850 plus births, Level II Nursery, one office, no HMOs! Call Georgetta: (800) 328-3666.

MAINE — Pediatric hematologist/oncologist. Join well-established, hospital-based pediatric service affiliated with 400-bed tertiary center serving over 400,000. Joint medical school appointment. P.O.G.-satelite. University community. One hour from coastal resorts; two hours from premier ski area. One hour flight from Boston. Competitive salary and benefits. Send CV to: New England Health Search, 63 Forest Avenue, Orono, ME 04473. Or call: (207) 866-5680 or (207) 866-5685.

VIRGINIA — Three person pediatric group seeks BE/BC pediatrician interested in full-time, primary care oriented practice in a growing community near the Blue Ridge Mountains. Contemporary office, friendly staff, easy access to metropolitan DC area. Box #112, c/o AJDC.

NEW JERSEY: Full-time/part-time, BC/BE pediatrician to join five-person, established pediatric practice, situated close to New York City. On staff of excellent community hospital with major university affiliation and pediatric house staff. Reply to: Box 312, Tenafly, NJ 07670.

WASHINGTON — Established, four full-time/two part-time pediatric group seeking full-time BC/BE pediatrician. Beautiful, rapidly growing community in midst of mountains and water, one hour from Seattle. Local hospital and nearby childrens' hospitals. Opportunity to practice a wide range of pediatric skills. Competitive salary; early partnership. Reply with cover letter and CV to: Medical Director, 2625 Wheaton Way, Suite A, Bremerton, WA 98310. (206) 479-1651.

PEDIATRICIAN — Expanding multi-specialty group practice in the San Diego area seeks third board-certified pediatrician. Excellent starting salary plus benefit package including professional liability insurance, three weeks paid vacation, relocation allowance, one week CME time, CME allowance, cafeteria plan for dependent child care, ESOP. Send CV to: Physician Recruitment, Inland East Medical Clinic, Inc., 10201 Mission Gorge Road, Suite L, Santee, CA 92071. (619) 449-4822, Extension 279.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

PEDIATRICIAN with neonatology fellowship experience to join pediatric group. Central New Jersey, 1½ hours New York City, Philadelphia, beaches, skiing. 443-bed community teaching hospital. Assistance with start-up costs. Send CV to: Box #113, c/o AJDC.

PEDIATRICIAN to join busy, small group practice. Town of 100,000, one hour north of San Francisco. Call shared with other pediatricians. Guaranteed salary leading to partnership. Send CV to: Pediatrics, 990 Sonoma Avenue, #5, Santa Rosa, CA 95404.

PEDIATRICIAN with training in behavioral and/or developmental pediatrics. Part-time. Resident supervision of behavioral curriculum development in primary care pediatric training program. Call or write: Dr. Emalee Flaherty, MD, Columbus Hospital, 2520 Lakeview, Chicago, IL 60614. (312) 883-5908.

FLORIDA HORSE COUNTRY — BC/BE pediatrician to join highly respected and active three-member group in developing area. Excellent opportunity. Send CV to: John M. Brinsko, MD, Ocala Pediatrics, 1500 SE 17th Street, Building 600, Ocala, FL 32671.

OBERLIN, OHIO — Multi-specialty group seeks BC/BE pediatricians to serve growing patient load. Northern Ohio college town serving drawing area of 275,000. Salary, liberal benefits first year with full shareholder status available thereafter. Send CV to: Dr. VanDyke, 224 West Lorain, Oberlin, OH 44074.

PEDIATRICIAN — Philadelphia suburbs. Want partner, not employee, for thriving three-person practice. Start November 1990. $75,000 package. Box 41012, Philadelphia, PA 19127-0012.

Pediatrician

We are seeking a BC/BE, energetic Pediatrician to join one other in an inpatient unit for technologically-dependent and chronically ill children. Solid knowledge base in general pediatrics and ventilator management is needed. We are affiliated with UCONN School of Medicine and provide teaching and research opportunities. We offer a highly competitive salary and excellent benefits.

Please send CV to: Christine Hart, M.D., The New Britain Memorial Hospital, 2150 Corbin Avenue, New Britain, CT 06053. E.O.E. M/F/H/V.

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Immediate opportunity to associate with five pediatricians in a 70-doctor multi-specialty group. Drawing area of 400,000. Modern hospital within five minutes of clinic. Stimulating Big-10 university community of 110,000 with superb cultural advantages. Ideal for families. Medical school teaching affiliation if desired. Excellent initial guarantee and fringes with early associate status, subsequent income based exclusively on productivity. Send CV to:

RONALD H. DEERING, MD
Christie Clinic Association
101 West University
Champaign, IL 61820

UTAH — BC/BE pediatrician needed in busy, 18-member multi-specialty group in Logan. Beautiful northern Utah university town. Guaranteed salary with incentive and benefits. Great family oriented and recreational opportunities. Send CV to: Neal Byington, Administrator, Budge Clinic, 225 East 400 North, Logan, UT 84321. (801) 752-0422.

Regional medical center for 85,000 population needs pediatricians; located in beautiful mountainous eastern Kentucky with state parks and lakes within thirty miles. Progressive community with excellent accredited school system. Active staff, 60 practicing physicians. If interested, send CV to:

Dr. John Tummons, Administrator
Methodist Hospital of Kentucky
911 South Bypass, Pikeville, KY 41501

BC/BE PEDIATRICIAN to join three pediatricians in university-run ambulatory center with regional hospital and university medical center affiliation, with emphasis on primary care. UMMC is an equal opportunity/affirmative action employer. Location: Southcentral Massachusetts. Appointment in university department of pediatrics. Membership in university group practice. Fringe benefits excellent. Salary negotiable. Reply: David P. Tapscott, MD, 281 East Hartford Avenue, Uxbridge, MA 01569-9658.

Southeast Wisconsin

PEDIATRICIAN to join 5 physician pediatric department in a 34 physician multi-specialty clinic. Service area population of 275,000 people. Near larger metropolitan area. Utilizing 2 hospitals (244 and 216 beds) Level II+ neonatal center and one of Wisconsin's largest pediatric departments. Contact Bob Strzelczyk at 1-800-243-4353.

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PHILADELPHIA AREA: Three pediatricians seeking BE/BC fourth in a growing suburban community. One office, minutes from hospital. Full partnership opportunity after two years. Convenient access to Philadelphia; recreational opportunities in nearby Pocono Mountains, and/or New Jersey beaches. Reply to: Box #115, c/o AJDC.

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Yi-Chuan Ching, MD, Chief
Department of Pediatrics
Kaiser Permanente
Medical Center
3288 Moanalua Road,
Honolulu, HI 96819

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TEXAS — BE/BC pediatrician to join busy, three-pediatrician group in Dallas/Fort Worth Metroplex. Competitive salary, incentives and benefits. Contact: Dan Geppert, MD, 950 North Davis, Arlington, TX 76012. (817) 460-0104.

LOUISIANA

Seeking board-certified or board-eligible pediatricians to provide part-time or full-time ambulatory services.

Responsibilities may include emergency room, child sexual abuse, transport, house coverage, or other services based on interest.

Our 153-bed hospital, Louisiana's only full service pediatric facility, provides multi-disciplinary care to patients from Louisiana and the Gulf South.

New Orleans offers a warm climate, a variety of entertainment and leisure activities, and the country's best food and music.

Louisiana license or qualification for licensure required. For consideration, send CV to:

Alan Robson, MD
Medical Director
Children's Hospital
200 Henry Clay Avenue
New Orleans, LA 70118

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TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. Please call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. AJDC-9834, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800)777-4912. Equal Opportunity Employer

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Pediatric Subspecialists

The University of South Dakota School of Medicine currently has openings for the following BE/BC pediatric subspecialties:

Cardiology **Neurology**
Pulmonology **Surgery**
Hematology/Oncology **Neonatology**
Intensivist **Infectious Disease**

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the healthcare of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

Sioux Falls is located in the geographic center of America with friendly people who exemplify traditional midwestern values. Our community has a strong economic base, growing population and a progressive educational system. Included in David Frankes' book, *America's Fifty Safest Cities*, Sioux Falls also offers numerous cultural opportunities. South Dakota's four season climate welcomes endless recreational activities year-round.

Competitive financial packages offered. EOE/AAE.

Send CV or call:
Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

Wisconsin

Pediatrics BE/BC

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The Monroe Clinic associates practice medicine without the distractions of office management. There is no financial investment and you will have easy access to high quality peers or specialists for consultation. Associates enjoy regular hours with call sharing and predictable time off for continuing medical education and vacations.

For an early prescription to a lasting, equitable partnership, please call or send your curriculum vitae to Robert Enterline, Physician Staffing Director, The Monroe Clinic, 1515 Tenth Street, Monroe, Wisconsin 53566.

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Professional Opportunities

COLORADO — BC/BE pediatrician to join seven-pediatrician department of established, multi-specialty clinic. Contact: Jos. L. Corrigan, MD, 209 South Nevada Avenue, Colorado Springs, CO 80903. (719) 475-7700.

NEW YORK — PEDIATRICIAN(S) wanted to join new practice on South Shore Long Island, forty-five minutes from New York City. Immediate partnership available for person interested in working practice and supplementing by working nearby ER part-time. Box #116, c/o AJDC.

PEDIATRIC NEUROLOGY TRAINING PROGRAM at Jefferson Medical College of Thomas Jefferson University, The Alfred I. duPont Institute and the Medical Center of Delaware is accredited and leads to certification in neurology with special competence in child neurology. Our program will consider applicants who will complete two years of residency in pediatrics by June 30, 1991. (Med/Peds residency may also meet requirements for eligiblity.) Clinical and basic research opportunities are available and encouraged. Send CV to: Leonard J. Graziani, MD, Thomas Jefferson University Hospital, 111 South Eleventh Street, Suite 8091, Philadelphia, PA 19107. Telephone: (215) 955-6822. Thomas Jefferson University Hospital is an equal opportunity/affirmative action employer.

TEXAS — BE/BC pediatrician to join busy, three-pediatrician group in Dallas/Fort Worth Metroplex. Compeititve salary, incentives and benefits. Contact: Dan Geppert, MD, 950 North Davis, Arlington, TX 76012. (817) 460-0104.

PEDIATRICIAN — BE/BC to join three others to cover pediatric unit, newborn ICU and delivery suite in large, progressive, community hospital, with excellent subspecialty support. Competitive salary with liberal fringe benefits including malpractice insurance, paid vacation, education leave and expenses, and health insurance. If interested, please contact: Gordon Borkat, MD, (216) 476-7237. Or send CV to: 18101 Lorain Avenue, Cleveland, OH 44111.

Neonatologist

The Medical Center at Princeton, a 450-bed community teaching hospital with a Level II Nursery, is seeking a second neonatologist for our expanding service at the Medical Center. Candidates should be board certified/eligible. Opportunity for medical school appointment. Send curriculum vitae and letter of interest stating salary expectations to:

Neonatologist Search Committee
c/o Administration
253 Witherspoon Street
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Professional Opportunities

NEWPORT, VERMONT: Board-certified, solo practitioner seeks BE/BC associate to join a rapidly growing solo practice, early partnership possible. Beautiful, rural, northern Vermont. Challenging patient load. Good university affiliations. Reply: T.A.E. Moseley, MD, North Country Hospital, Newport, VT 05855.

Positions Available

THE DEPARTMENT OF PEDIATRICS at the Allegheny Campus of the Medical College of Pennsylvania is seeking BC/BE pediatricians to provide inpatient coverage for hospitalized children. It is an exciting opportunity to provide care for pediatric patients with a wide variety of acute and chronic illnesses. Other duties include teaching medical students and residents. Research opportunities are available. If interested send curriculum vitae or contact: Adrian Dana, MD, Director Inpatient Pediatrics, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212. Telephone: (412) 359-3161.

Residencies

PL-3 RESIDENT POSITIONS available July 1, 1991. Due to illness and career change, the Children's Hospital of Pittsburgh will have two (2) openings at the PL-3 level for July 1, 1991. The year provides an excellent supervisory experience in general pediatrics along with the opportunity for electives in all major subspecialty areas. Please contact: J. Carlton Gartner, Jr, MD, Director-Pediatric Residency Program; The Children's Hospital of Pittsburgh, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213. (412) 692-5107.

IVY LEAGUE MEDICAL STUDENT seeks partner to share pediatric internship or residency in Boston beginning July 1991. Reply: (617) 731-5982 or P.O. Box 67290, Chestnut Hill, MA 02167.

PEDIATRICS — Residency position. PL-III position available beginning July 1991 in fully accredited program at the University of Florida College of Medicine. Broad inpatient and ambulatory experience in general pediatrics and all subspecialites. Completion of PL-I and PL-II years at an approved program is required. Ideal location in rapidly growing area of north central Florida with outstanding recreational opportunities. Interested individuals should contact: Lynn Kutsche, MD, Residency Director, or Robert Fennell, MD, Chairman, H/S Recruiting, Department of Pediatrics, JHMHC Box J-296, Gainesville, FL 32610.

Faculty Positions

CALIFORNIA — The Department of Pediatrics, UCLA School of Medicine, is seeking neonatologists at the assistant or associate professor level to participate in a program in neonatal medicine at Los Angeles County Olive View Medical Center. Olive View is an integral part of the UCLA teaching and research program sharing house staff, faculty and facilities. The ability to obtain a California license is required. Applicants should send their curriculum vitae to: S. Douglas Frasier, MD, Chief of Pediatrics, Olive View Medical Center, 14445 Olive View Drive, Suite 3A108, Sylmar, CA 91342. Equal opportunity employer M/F.

PEDIATRICIAN/PEDIATRIC infectious disease specialist — The Division of Immunology and Infectious Disease, Department of Pediatrics, University of Miami School of Medicine invites applications for a position as an Assistant Professor of Clinical Pediatrics to provide direct patient care in the pediatric AIDS inpatient and outpatient units. Potential for involvement in ongoing clinical research protocols. Excellent opportunity for an individual with clinical and teaching skills in the setting of a large county teaching hospital. Training in pediatric infectious disease preferred but not required. Applicants should send a curriculum vitae in confidence to: Gwendolyn B. Scott, MD, Director, Division of Pediatric Immunology and Infectious Disease (D4-4), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101. The University of Miami is an affirmative action/equal opportunity employer.

Faculty Positions

PEDIATRIC HEMATOLOGIST/ONCOLOGIST — Loyola University of Chicago, Stritch School of Medicine, Department of Pediatrics, is recruiting an Assistant Professor for the Section of Hematology/Oncology. Applicant must be sub-board certified or eligible, with expertise in hematology/oncology research. Interested applicants are invited to send their CV to: Carlos R. Suarez, MD, Director, Section of Pediatric Hematology/Oncology, 2160 South First Avenue, Maywood, IL 60153. Loyola University of Chicago is an equal opportunity educator and employer. Qualified persons are not subject to discrimination on the basis of a handicap.

NEW YORK — NEONATOLOGIST. Department of Pediatrics, State University NY at Buffalo is seeking faculty member to join nine-member division of neonatology. Assistant professor level. BC in pediatrics, BE/BC in neonatology. Responsibilities include administrating and attending at the Level I program and attending at the Level III Intensive Care Nursery. Teaching of neonatology fellows; pediatric, obstetric and family medicine residents; and pediatric nurse practitioners is also included. The division conducts NIH sponsored laboratory research and clinical research including six years of experience with surfactant therapy. Contact: Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. (716) 878-7673. Affirmative action/equal opportunity employers.

AMBULATORY PEDIATRIC MEDICINE — The Division of Ambulatory Medicine, Children's Hospital of The King's Daughters, is seeking additional faculty beginning July 1991. Responsibilities include: resident and medical student teaching, direct patient care and clinical research. Outpatient visits for 1989-1990 totaled approximately 50,000. Academic appointment with Eastern Virginia Medical School commensurate with experience. Please contact: John M. de Triquet, MD, Children's Hospital of The King's Daughters, Ambulatory Pediatric Medicine, 800 West Olney Road, Norfolk, VA 23507. (804) 628-7179.

NEONATOLOGISTS

The Department of Pediatrics, University of Texas Medical School at Houston is seeking additional full-time faculty for the Division of Neonatal-Perinatal Medicine.

The division has an active fellowship training program, faculty with diverse research interests and excellent clinical facilities. Three distinct types of faculty appointments are available:

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2) An academic track centering on clinical investigative activities at one of our two, state-of-the-art, tertiary care care hospitals (Hermann Children's Hospital and Lyndon Baines Johnson General Hospital), and
3) A clinical track at one of three intermediate care units in community hospitals.

Applicants should be BC/BE in neonatal-perinatal medicine. Faculty rank commensurate with previous experience.

The University of Texas is an equal opportunity employer. Women and minorities are encouraged to apply.

Contact:

Susan E. Denson, MD
Department of Pediatrics
University of Texas Medical School
P.O. Box 20708
Houston, TX 77225 • (713) 792-5342

Faculty Positions

PEDIATRICIAN — Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

PEDIATRIC PATHOLOGIST — The Department of Pathology, Indiana University School of Medicine is seeking a fourth pediatric pathologist for James Whitcomb Riley Hospital for Children. The position is geographically located in the university teaching hospitals. Candidates must be board-certified as well as have fellowship training in pediatric pathology or equivalent experience. The academic rank and salary will be commensurate with experience and background. In addition to service responsibilities, the position will require the individual to participate in education programs of the department. A record of publications and investigative skills with a continuing program of active research is essential. This is a tenure track position. Indiana University is an equal opportunity employer. Send curriculum vitaes to: Stephen A. Heifetz, MD, Director, Division of Pediatric Pathology, James Whitcomb Riley Hospital for Children, 702 Barnhill Drive, Room 236, Indianapolis, IN 46202.

Fellowships

FELLOWSHIP IN DEVELOPMENTAL and behavioral pediatrics: Available July 1, 1991, one-two years duration. Emphasis on assessment and treatment of children with developmental disabilities and handicapping conditions in a community setting. The Waterbury Regional Department of Pediatrics is a primary care pediatric training program integrated with the University of Connecticut Department of Pediatrics. Independent research with the goal of publication is expected. Candidate must be license-eligible. Send inquiries to: Mark D. Simms, MD, M.P.H., 56 Franklin Street, Waterbury, CT 06706. An equal opportunity employer.

FELLOWSHIP
in Developmental/ Behavioral Pediatrics

The Alfred I. duPont Institute Children's Hospital, a multi-specialty pediatric hospital with a busy developmental pediatrics clinic, has a two year position for PL-IV available. Developmental disabilities, learning & behavior problems. Opportunity for teaching and clinical research. We offer an excellent compensation package; benefits include on-site daycare center. For consideration, contact: **Douglas M. Spencer, M.D., THE ALFRED I. duPONT INSTITUTE, P.O. Box 269, Wilmington, DE 19899.** Equal Opportunity Employer.

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Reference: 1. Lohninger A, Kaiser E, Legenstein E, et al: Carnitine, metabolism and function, in Kaiser E, Lohninger A (eds): *Carnitine—Its Role in Lung and Heart Disorders.* Basel, Switzerland, Karger, 1987, p 4.

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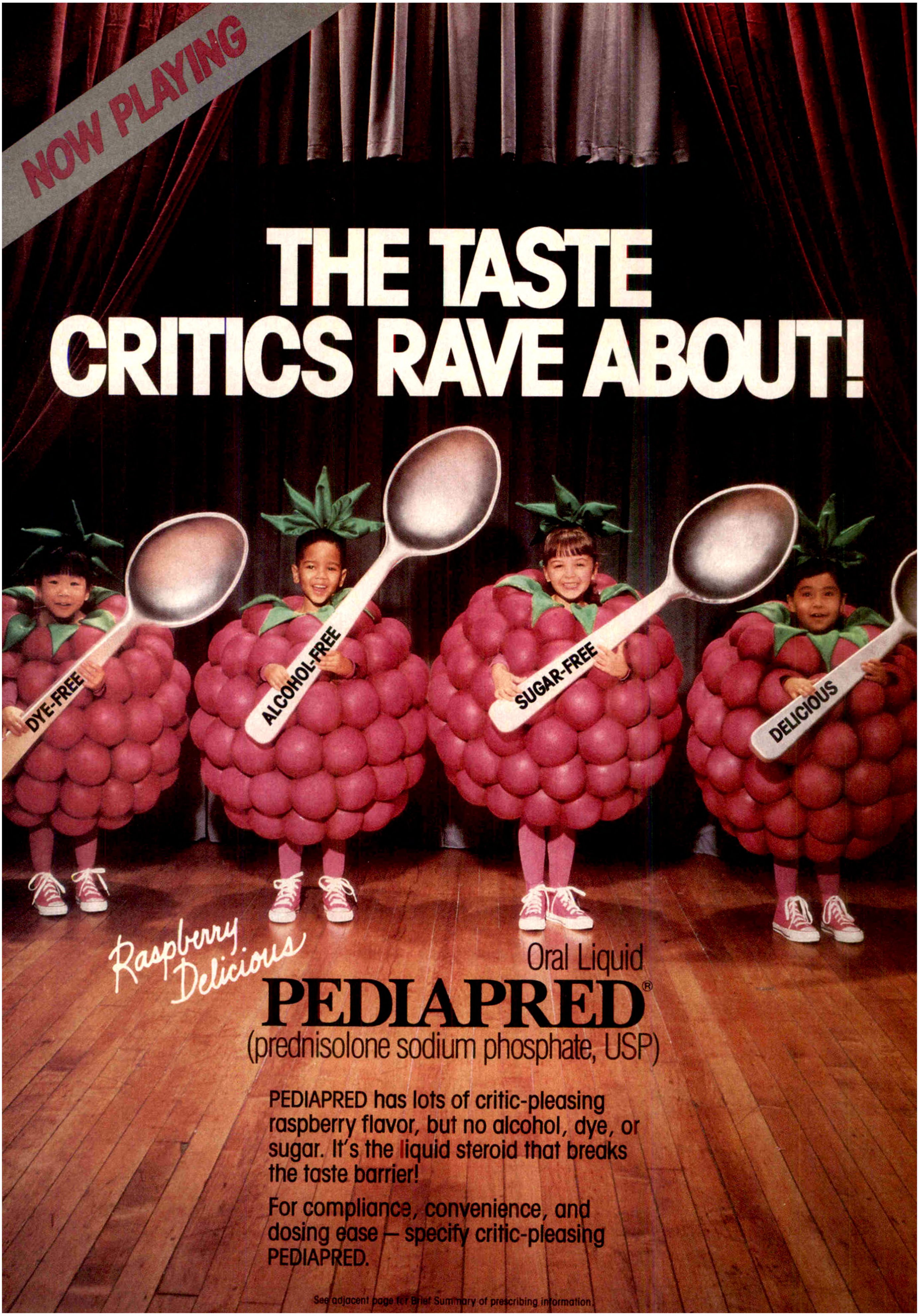

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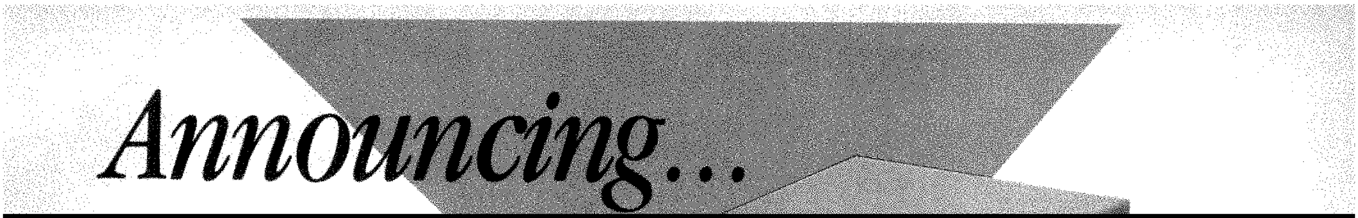

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The Editorial Board Speaks . . .

Laurence Finberg, MD

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Racial, Social, and Environmental Risks for Childhood Asthma

Michael Weitzman, MD; Steven Gortmaker, PhD; Arthur Sobol, MA

• Unlike a number of childhood problems, it is not clear that there are racial or socioeconomic disparities in the prevalence of childhood asthma. We analyzed data from the Child Health Supplement to the 1981 National Health Interview Survey, a population-based survey with information concerning 15 416 children, to address the following questions: are there racial or socioeconomic differences in rates of childhood asthma; if yes, what is the contribution of social and environmental characteristics to the observed differences? In this sample, black children were more likely to have asthma than were white children (4.4% vs 2.5%). Racial disparities in prevalence emerged early and at all childhood ages were due to higher black rates of onset between the ages of 1 and 3 years. Poverty status, maternal cigarette smoking, large family size, smaller size of home, low birth weight, and maternal age younger than 20 years at the child's birth were all associated with increased rates of childhood asthma. When available social and environmental characteristics were controlled for using multivariate analyses, the increased risk for asthma among black and poor children was reduced to statistical insignificance. We conclude that black and poor children in the United States do have higher rates of asthma, that social and environmental factors exert substantial influences on rates of asthma, and that much of the racial and economic disparity in prevalence can be accounted for by a variety of social and environmental characteristics.

(*AJDC.* 1990;144:1189-1194)

Asthma is the most common chronic illness of childhood,[1] but our understanding of its prevalence in various populations and factors related to differential rates of occurrence is still incomplete. Much of what is known about asthma is derived from clinical rather than population-based studies.[2] The samples from these studies, and thus their findings, are subject to many potential biases, and many basic questions about asthma remain unanswered.

For example, the relative contributions of environmental and genetic influences to the prevalence of asthma remain unclear. Identification of social and environmental influences is important because it can provide clues to prevention and more effective treatment. Previous studies have convincingly demonstrated a genetic component.[3,4] Certain children are clearly susceptible, but susceptibility does not confer uniform occurrence or expression of the condition. For example, a Scandinavian study of 7000 pairs of twins found that the frequency of concordance for asthma was only 19% in monozygotic twin pairs and 5% in dizygotic pairs, suggesting that genetic factors, although influential, may be less important than environmental factors in the clinical expression of asthma.[4] It seems that a predisposition to airway hyperreactivity is inherited, but some environmental factor is required before this predisposition is translated into asthma.[2]

Unlike a number of childhood problems, such as low birth weight, infant mortality, lead poisoning, and human immunodeficiency virus infection, it is not clear that there are racial or socioeconomic disparities in the prevalence of childhood asthma. Recent reports indicate that the prevalence of asthma and asthma-related hospitalizations and deaths in the United States are increasing,[5-7] and a number of studies suggest that these trends are occurring primarily among black children and youth.[5,6,8-10] One recent study demonstrated that differential hospitalization rates for asthma in black and white children are in part accounted for by differences in family income.[11] Another, using data from the National Health and Nutrition Examination Surveys, found that the prevalence of childhood asthma is increasing in the United States and that black children are more likely to have asthma than are white children.[5]

We analyzed data from the Child Health Supplement to the population-based 1981 National Health Interview Survey to address the following questions: (1) Are there racial disparities in the prevalence of childhood asthma? (2) Are there social or environmental characteristics of children that are independently associated with an increased risk of asthma? (3) If 1 and 2 are true, is there evidence that social or environmental characteristics are responsible for all or part of the observed racial disparities in the prevalence of childhood asthma?

SUBJECTS AND METHODS

Data from the Child Health Supplement to the 1981 National Health Interview Survey were used in these analyses. The National Health Interview Survey employs a complex, multistage probability sampling design to provide a representative sample of the civilian noninstitutionalized population of the United States.[12] The 1981 survey included a Child Health Supplement, which collected data on one randomly selected child in each eligible household and included 15 416 children aged from birth to 17 years. The interview contained a series of questions concerning children's chronic health conditions and family sociodemographic characteristics. All information was derived from parent reports; there were no medical examinations of children or review of medical records.

Variables

Asthma Definition and Categories.—Parents (generally the mother) were read a list of 59 chronic health conditions, including

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From the Department of Pediatrics, Boston City Hospital, and Boston University Schools of Medicine and Public Health (Dr Weitzman), and the Harvard School of Public Health (Dr Gortmaker and Mr Sobol), Boston, Mass. Dr Weitzman is now with the University of Rochester (NY) School of Medicine and Dentistry.

Read in part at the 29th Annual Meeting of the Ambulatory Pediatric Association, Washington, DC, May 5, 1989.

Reprint requests to Department of Pediatrics, Rochester General Hospital, 1425 Portland Ave, Rochester, NY 14621 (Dr Weitzman).

asthma, that their child might have. Children were identified as currently having asthma if their parents reported that it was present at the time of the interview, had been present for longer than 3 months, and had not been cured. Parents were also asked how old the child was when asthma was first noted. A separate series of questions ascertained whether the child had taken a physician-prescribed asthma medication in the past 2 weeks. In the current analysis, children reported as having taken such a medication were categorized as current users of asthma medications.

The majority of population-based studies of childhood asthma have relied on parental reporting for identifying children with asthma. While studies have found that parental reports tend to overestimate the prevalence of clinically diagnosed chronic conditions, overreporting tends to decline with the severity or perceived stigma of the conditions.[13,14] Some authors believe, however, that exclusive dependence on physician reporting results in significant underreporting of childhood asthma.[15] In one study, 96% of school-aged children with asthma could be identified by parental reports[15]; in another, parental reports of children's asthma were confirmed in 94% of cases[10]; and another study demonstrated that parent reports of childhood asthma are a good indicator of impaired ventilatory function.[16]

Social, Environmental, and Behavioral Variables.—The racial, social, and environmental characteristics investigated included race, family income, maternal education, maternal age during pregnancy, residence with both biologic parents, family size, number of rooms in household, an index of crowding (family size divided by number of rooms), urban vs rural residence, geographic region, and breast-feeding. Two racial categories (white and black) were used in these analyses. We defined an income poverty variable based on income category and family size as defined by the federal government.[17] The 1980 total family income was used, adjusted for the consumer price index. Because the income categories in the National Health Interview Survey were broad, this poverty measure was focused on extreme poverty to ensure that all children classified in this category were in fact living in poverty. Other risk variables investigated included the child's age, gender, nights spent in a neonatal intensive care unit after birth, and low birth weight (<2500 g). Questions were also asked about maternal smoking during pregnancy for all sample children aged 0 to 5 years. Other studies have demonstrated stability of maternal smoking from pregnancy until early childhood.[18,19] That is, women who smoke during pregnancy tend to continue to smoke following pregnancy, and thus the measure of maternal smoking employed in these analyses may reflect both prenatal and postnatal exposures.

Table 1.—Estimated Prevalence of Asthma and Use of Asthma Medications by Age and Age at Onset According to Race, United States, 1981

	White, %	Black, %	*P*
Asthma			
Age, y			
0-17 (n = 15 224)	2.5	4.4	.0001
2-5 (n = 3093)	3.1	6.5	.0001
6-17 (n = 10 386)	2.6	4.0	.002
Age at onset, y			
0-5	1.7	3.1	.001
6-17	0.8	0.4	.16
Use of asthma medications			
Age, y			
0-17	0.8	1.5	.003
2-5	0.8	1.4	.19
6-17	0.9	1.6	.03
Age at onset, y			
0-5	0.6	1.2	.005
6-17	0.3	0.2	.35

Statistical Analyses

All survey responses were weighted when calculating proportions and conducting the logistic regression analyses using the weights provided by the National Center for Health Statistics, which reflect the probability of selection, nonresponse, and poststratification adjustments. We used χ^2 tests to test for differences in proportions. Logistic regression analyses were conducted to identify independent risk factors for asthma using the PC SAS CATMOD program. The regression coefficient estimates can be interpreted as odds ratios (ORs) associated with the predictor variable. Multivariate logistic regression models were estimated by first controlling for race, gender, maternal smoking, and low birth weight. Additional variables were added to the model if they were associated with a *P* value below .05. Some variables that initially had many categories (eg, family size) were changed to dichotomous variables to simplify data presentation.

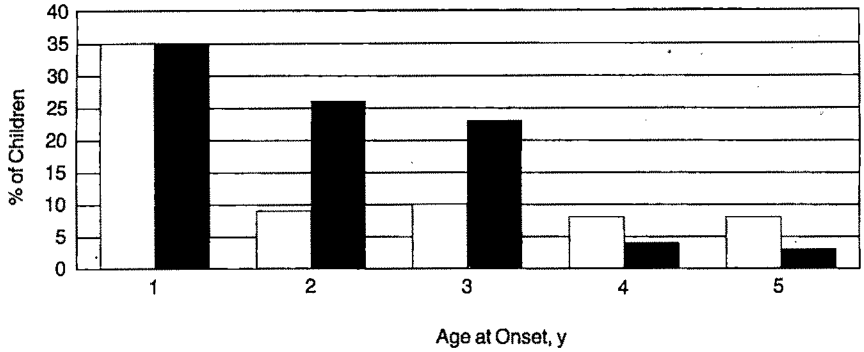
Estimates of statistical significance were made assuming simple random sampling. The actual sampling design was stratified, multistage, and clustered, so the assumption of simple random sampling can overestimate statistical significance. The effects of this clustering will be to overstate significance levels slightly. For this reason, we are cautious in discussing associations significant only at the *P* = .05 level.

RESULTS

Of the total sample of 15 416 children aged 0 to 17 years, 432 (2.8%) were reported as currently having asthma. Thus, an estimated 2.5% of all white children in the United States have asthma as compared with 4.4% of black children (*P* = .0001; Table 1). When children younger than 2 years old were excluded because of concern that parents might mistakenly report respiratory illnesses associated with wheezing as asthma in this age group, and then children were categorized into age groups 2 to 5 and 6 to 17 years, black children in each group were more likely to have asthma than white children: 6.5% vs 3.1% (*P* = .0001) for ages 2 to 5 years and 4.0% vs 2.6% (*P* = .002) for 6 to 17 years.

Among children aged 6 to 17 years, racial differences were exclusively due to increased rates among black children in the subset who had their onset before the age of 6 years (3.1% vs 1.7%; *P* = .001). Among children aged 6 to 17 years who had their onset after their sixth birthday, there were no statistically significant racial differences in rates of asthma.

Racial variations among children reported as current users of asthma medications were similar to those found for children reported as having asthma. Among children aged 0 to 17 years, 1.5% of black children were reported as current users of asthma medications as compared with 0.8% of white children (*P* = .003). For children aged 2 to 5 years, 1.4% of black children were re-



Age at onset of asthma among children aged 6 to 17 years in the United States, 1981. White bars indicate white children; black bars, black children.

ported as current users as compared with 0.8% of white children ($P = .19$). Current use of asthma medication in children aged 6 to 17 years was reported in 1.2% of black children vs 0.6% of white children ($P = .005$) among those reported as having the onset of asthma before the age of 6 years, whereas among those with onset of asthma after their sixth birthday, there were no racial differences (0.2% of black children vs 0.3% of white children; $P = .35$).

The Figure highlights racial differences in age at onset of asthma among children aged 6 to 17 years. More than 80% of all children aged 6 to 17 years with asthma in the United States were reported as having the onset in the first 5 years of life: 71% of white children and 90% of black children. Thus, racial disparities in the prevalence of asthma emerged early. There was no racial difference reported in onset in the first year of life; the racial difference in prevalence among this sample was due to black children's having a higher rate of onset of asthma in the second and third years of life.

Because of the importance of asthma with onset before the age of 6 years, we attempted to identify social and environmental characteristics that predict asthma at younger ages, particularly the ages of 2 to 5 years. The reported prevalence of asthma by selected characteristics of children aged 2 to 5 years is given in Table 2. Asthma was more common among children with the following characteristics: black race (unadjusted OR = 2.2); male gender; children whose mothers smoke half a pack of cigarettes or more per day; children with birth weights less than 2500 g or who spent 1 or more nights in a neonatal intensive care unit; children whose mothers were less than 20 years of age at their birth or who had less than a high school education; children from large families (six or more people living together) or who do not reside with both biologic parents; and those who live in poverty (each significant at $P \leq .02$). Living in a large home (eight or more rooms) was associated with reduced rates of asthma among children aged 0 to 5 years. Whereas our index of crowding was not associated with asthma prevalence, both a large family and small living space were associated with increased rates of asthma.

Although not statistically significant, black-white differences in rates of use of asthma medications were similar to those observed for asthma prevalence, and the lack of statistical significance may be due to the small number of children using these medications in this sample. Even with small numbers, however, certain variables were still strongly associated with current use of asthma medications, namely, maternal smoking ($P = .0001$), low birth weight ($P = .003$), having spent 1 or more nights in a neonatal intensive care unit ($P = .001$), and large family ($P = .0001$).

Table 3 describes the results of multivariate logistic regression analyses conducted to identify characteristics of children aged 2 to 5 years that are independently associated with an increased risk of asthma. In the first regression analysis, we controlled for male gender, maternal smoking, low birth weight, large family size, large house, and low maternal education. The ORs demonstrate the independent contribution of each variable to the prediction of childhood asthma. All were independently associated with an increased risk of asthma ($P < .05$). In this analysis, black children were 1.7 times as likely to have asthma as were white children ($P = .03$).

The second half of Table 3 demonstrates the results of similar analyses that included an additional variable indicating residence with only one biologic parent and another variable for extreme poverty. Residence with only one biologic parent was associated with an increased risk of childhood asthma (OR = 1.4), but this association is not statistically significant ($P = .15$). Similarly, extreme poverty was associated with an increased risk of asthma (OR = 1.3), but again this association is not statistically significant ($P = .39$). When these two variables are included in the regression analysis, the OR associated with being black is reduced to 1.5, which also is not statistically significant ($P = .13$). Clearly, race, poverty, and single-parent households are variables that are substantially correlated. By controlling for these three simultaneously, one effect of this multicollinearity is to reduce all the coefficient estimates to statistical insignificance. These results provide further evidence of the confounding of race and socioeconomic variables.

Although not shown, in none of the many analyses performed was breastfeeding found to add predictive power to these regressions, and there was no independent contribution of urban vs rural residence or region of the United States. Moreover, when similar analyses were carried out for children aged 6 to 17 years with an onset of asthma after the age of 5 years, none of the available social or environmental variables were statistically significant predictors of asthma.

COMMENT

The 1981 Child Health Supplement to the National Health Interview Survey provided the opportunity to study childhood asthma using a population-based sample. Data from this survey clearly indicate that black children have significantly higher rates of asthma than do white children in the United States at all ages after the first year of life and that racial disparities emerge early and are

Table 2.—Reported Prevalence of Asthma and Current Use of Asthma Medications by Selected Characteristics of Children Aged 2 to 5 Years*

Characteristic (n)	Asthma		Asthma Medication Use	
	%	P	%	P
Race (3093)				
B (14.5%)	6.5	.0001	1.4	.19
W (85.5%)	3.1		0.8	
Gender (3093)				
M (51.0%)	4.4	.01	1.2	.06
F (49.0%)	2.7		0.6	
Maternal smoking, PPD (2729)				
≥1/2 PPD (13.0%)	6.4	.002	2.6	.0001
<1/2 PPD (87.0%)	3.2		0.6	
Birthweight, g (2927)				
<2500 (7.4%)	8.3	.0001	2.8	.003
≥2500 (92.6%)	3.4		0.8	
NICU stay ≥1 night (3093)				
Yes (10.9%)	5.8	.02	2.4	.001
No (89.1%)	3.3		0.7	
Maternal age at birth, y (3093)				
<20 (15.2%)	5.7	.007	0.7	.59
≥20 (84.8%)	3.2		0.9	
Maternal education (3093)				
<High school (23.9%)	5.9	.0001	1.4	.18
≥High school (76.1%)	2.8		0.7	
Family size (3093)				
≥6 (17.1%)	5.7	.003	2.2	.0001
<6 (82.9%)	3.1		0.6	
Size of house, rooms (3093)				
≥8 (15.1%)	1.2	.003	0.3	.14
<8 (84.9%)	4.0		1.0	
Extreme poverty (3093)				
Yes (18.2%)	6.0	.001	1.5	.10
No (81.8%)	3.0		0.8	
Residence with both parents (3093)				
Yes (74.9%)	3.0	.003	0.8	.31
No (25.1%)	5.2		1.2	
Breast-fed (3093)				
<6 mo (9.9%)	3.4	.59	1.6	.44
6 mo-1 y (13.1%)	3.0		0.5	
>1 y (13.6%)	2.7		1.2	
No (63.5%)	3.9		0.8	
Urban vs rural residence (3093)				
Urban/central city (25.8%)	4.2	.42	1.2	.41
Suburban (40.2%)	3.1		0.9	
Rural/smaller cities (34.1%)	3.6		0.6	
Region (3093)				
Northeast (20.6%)	3.3	.76	0.2†	.20
North central (27.3%)	3.4		0.9	
South (32.1%)	4.1		1.2	
West (19.7%)	3.2		1.1	

*PPD indicates packs of cigarettes per day; NICU, neonatal intensive care unit. Sample sizes vary because response rates for individual questions vary.

†Fewer than five in cell.

associated with increased rates of onset of asthma among black children between the ages of 1 and 3 years. While these data indicate that a number of physical characteristics of children, such as male gender and low birth weight, are highly associated with the prevalence of asthma, asthma is also more common among children living in poverty, and social and environmental characteristics appear to exert substantial influences on rates among children who have their onset of asthma before the age of 6 years.

The limitations of these data should be acknowledged. The data were not prospective, and thus one must be cautious about drawing causal inferences. The exclusive measure of childhood asthma was parental reporting. Physical examinations would not necessarily have resulted in more accurate identification of children with asthma, however, since signs and symptoms of asthma are often intermittent, and many children with asthma have normal baseline respiratory status between attacks. Similarly, information from medical records is notoriously incomplete. Moreover, the relationships among rates of asthma, children's racial status, and age at onset of asthma persist among the subset of children who were clearly believed to have asthma by physicians, that is, those reported as current users of asthma medications. There were also only a limited number of social, environmental, and health-related characteristics to investigate. For example, little information was available about family history of asthma or the prenatal and perinatal histories of mothers and children, and no information was available about differences in antigenic exposures. Only families with children less than 5 years old were asked about maternal smoking, and questions were only asked about prenatal smoking. Since women who smoke during pregnancy tend to continue to smoke following pregnancy,[18,19] the estimate of children's exposure to cigarette smoke does not enable us to distinguish prenatal from postnatal effects. Also, the number of children with onset of asthma between the ages of 6 and 17 years was small. Among children aged 6 to 17 years with onset of asthma before the age of 6 years, responses to social and environmental questions refer to their situation at the time of the interview and may not reflect their situation at the time asthma was developing.

Black children in the United States have been found to have higher rates of asthma than white children in several previous studies.[5,10,20] Nonwhite chil-

Table 3.—Logistic Regression Results: Independent Predictors of Childhood Asthma, Ages 2 to 5 Years*

	Odds Ratio	95% Confidence Interval	*P*
	First Analysis		
Black	1.7	1.1-2.8	.03
Male	1.8	1.2-2.7	.008
Maternal smoking (≥1/2 pack/d)	1.9	1.2-3.2	.01
Low birth weight (≤2500 g)	2.0	1.1-3.5	.02
Large family (≥6)	1.8	1.1-2.9	.02
Large house (≥8 rooms)	0.26	0.09-0.74	.01
Low maternal education (<high school)	1.7	1.1-2.6	.02
	Second Analysis		
Black	1.5	0.9-2.5	.13
Male	1.8	1.2-2.7	.008
Maternal smoking	1.9	1.2-3.1	.01
Low birth weight	2.0	1.1-3.5	.02
Large family	1.9	1.2-3.1	.01
Large house	0.27	0.10-0.76	.01
Residence with only 1 biologic parent	1.4	0.8-2.2	.15
Extreme poverty	1.3	0.9-1.7	.39

*In the first analysis, we controlled for male gender, maternal smoking, low birth weight, large family, large house, and low maternal education. In the second analysis, we included additional variables indicating residence with only one biologic parent and extreme poverty. This change highlighted the confounding variables of race and socioeconomic variables.

dren were 1.3 times as likely to have asthma as were white children in the 1970 National Health Survey.[20] In the second National Health and Nutrition Examination Survey (1976 to 1980), black children were 1.5 to 1.7 times as likely to have asthma as white children, depending on the definition of asthma employed.[5] A smaller study of asthma among children in the first and sixth grades in Baltimore, Md, also found that black children were 1.5 times as likely to have asthma as white children.[10] Factors leading to racial differences, however, remain unclear, and previous reports have not related racial differences in prevalence to differences in age-specific rates of onset or social or environmental characteristics of children.

Two novel and intriguing observations derived from this data set are that (1) there are no racial differences in prevalence of asthma in the first year of life, and (2) all racial differences are due to differences in rates of onset between the ages of 1 and 3 years. The available data do not directly account for these findings. One possible explanation is that differential rates of asthma are due to differences in environmental exposure between black and white children in the first years of life. The comparable rates in their first year may be due to the need for a period of exposure to an environmental irritant or allergen before asthma develops; ie, some children may require a period of exposure or an exposure that does not occur until the latter part of the first year, or the second or third year, for asthma to develop. Alternately, it is possible that there is a genetic basis for black-white differences both in rates and age at onset that is not dependent on environmental exposure. The finding, however, that the increased risk of asthma among black children is reduced to a statistically insignificant level when social and environmental characteristics are controlled would seem to refute this interpretation.

These data provide no evidence that breast-feeding is associated with a reduced prevalence of asthma. Although there have been many studies of the role of breast-feeding in the prevention of atopic disease (eczema, hay fever, and asthma), the evidence remains equivocal, and as regards asthma in particular, many studies report no benefits.[21-25] Similarly, the association between rates of childhood asthma and urban vs rural residence and region of the United States is still unclear. A recent study using data from the second National Health and Nutrition Examination Survey found that urban residence is associated with increased rates of childhood asthma.[5] The definition of asthma employed in that study, however, was broader than the one used in the current study (asthma in that study was defined as a current history of the disease that was diagnosed by a physician sometime in the past and/or frequent trouble with wheezing during the past 12 months). It is possible that the broad definition resulted in the inclusion of a wider range of respiratory problems that may be associated with urban residence, thus falsely suggesting a relationship between urban residence and rates of childhood asthma. Although we did not demonstrate this association, the trend in the data reported in the current study was in a similar direction, and it is possible that with a larger sample or more inclusive definition we too might have demonstrated that urban residence is associated with increased rates of childhood asthma.

The relationships between family size, crowding, and childhood asthma also remain unclear. At least two earlier studies[25,26] found no relationship between family size and rates of asthma, whereas one study found an increased severity of asthma in children from larger families.[27] Four previous studies showed no relationship between crowding and asthma,[16,26-28] and one study showed only a marginal effect.[5] In the current study, although a crowding index of numbers of people per room did not predict rates of asthma, children living in families with six or more people were almost twice as likely to have asthma, whereas residence in a large home was associated with a protective effect. Children living in homes with eight or more rooms had rates only one fourth those of children living in smaller homes. In this sample, children living in large families but not in large homes were almost seven times as likely to have asthma as were children living in smaller families and larger homes.

Several previous studies have found that poverty is associated with an increased prevalence of childhood illness and mortality,[29-32] but no consistent relationship has been demonstrated between socioeconomic status and the prevalence of childhood asthma. Low family income has been shown previously to be associated with underdiagnosis and decreased preventive care for children with asthma,[15] both of which may be associated with more severe symptoms and more frequent hospitalizations,[11] but its relationship to the prevalence of asthma has not been convincingly demonstrated. In fact, it is generally believed that asthma is more common among children in families of higher socioeconomic status.[29] At least six studies from the United Kingdom have found that childhood asthma is more common among families with higher occupational status[16,24,26,33,34]; five other studies, including two from the United States, have found no relationship between the prevalence of childhood asthma and family socioeconomic status.[5,10,25,27,28] In this study we found that children living in poverty have higher rates of asthma than those living in more affluent families. When entered into regression analyses that include a number of factors, each of which is highly associated with poverty, no independent effect of poverty was demonstrated in this data set. These results suggest that characteristics of a poverty-related environment, rather than income itself, contribute to much of the increased rates of asthma among children living in poverty.

The increased risk for asthma among black children in this sample also was gradually reduced to the point where it was no longer statistically significant as one controlled for low birth weight, maternal smoking status, and a variety of social and environmental characteristics. Although the characteristics investigated did not reduce the estimated OR associated with race to 1.0, we conclude that much of the observed racial disparity is due to social and environmental differences between black and white children in the United States.

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Bacteremia in an Ambulatory Setting

Improved Outcome in Children Treated With Antibiotics

Elizabeth R. Woods, MD, MPH; James L. Merola, PhD; William G. Bithoney, MD;
Howard Spivak, MD; Paul H. Wise, MD, MPH

• We undertook a study of 414 bacteremic patients (167 with *Haemophilus influenzae* and 247 with *Streptococcus pneumoniae* bacteremia) to evaluate their clinical presentation, laboratory and clinical results, and subsequent outcomes. Patients with *H influenzae* bacteremia were more likely to have soft-tissue foci, poorer clinical appearance at presentation, and be at higher risk for subsequent serious focal infections, persistent bacteremia, and subsequent hospital admissions than patients with *S pneumoniae*. Patients with *H influenzae* bacteremia had a 21.1-fold increase in risk of meningitis (95% confidence interval [CI] of 3.8 to 78.0) compared with those with *S pneumoniae*. The odds ratio for initial lumbar puncture was 5.25 (95% CI [1.1-23.6]). Ambulatory patients treated with antibiotics at presentation were less likely to develop new serious soft-tissue infections, persistent bacteremia, or to require subsequent hospital admissions than untreated patients. The effect of treatment was greater for patients with *S pneumoniae* than those with *H influenzae*. Careful follow-up and reevaluation of patients with presumptive bacteremia is essential because treated and untreated patients can still develop serious soft-tissue infections.

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Bacteremia has been shown to occur in 3% to 4% of febrile young children.[1-3] The incidence increases to 10% for children between 3 and 24 months of age with temperatures of 40°C or greater, white blood cell (WBC) counts greater than 15×10^9/L, or sedimentation rates greater than 30 mm/h.[1-7] Because patients with bacteremia may not have an identifiable source of infection and are still at risk for subsequent septic complications,[8-11] the primary care provider needs to be able to identify these patients and to treat them appropriately.

One previous study suggested that lumbar punctures (LPs) in bacteremic patients may increase the subsequent risk of meningitis.[12] In contrast, Shapiro et al[13] found that the risk of meningitis in bacteremic children was most strongly associated with the type of bacteremia rather than the performance of LPs. Because an LP is an essential test when examining some potentially bacteremic patients, it is important to identify the predictors of subsequent meningitis.

Several previous studies have suggested that antibiotic treatment favorably alters the clinical course of ambulatory bacteremias,[7,14] but this is still controversial.[15,16] Studying potentially bacteremic patients prospectively requires large cohorts of patients and multiple visits because the incidence rates of bacteremia in febrile children are small. Carroll et al[14] and Jaffe et al[15] randomly treated and followed up large numbers of febrile patients; however, because of the small numbers of bacteremic patients and subsequent new foci, their studies had very low power. To assess a large number of patients, this study was undertaken to evaluate the initial presentation, treatment, and outcome of all the patients with *Haemophilus influenzae* or *Streptococcus pneumoniae* bacteremia who presented to the emergency services of Children's Hospital, Boston, Mass, during a 4-year period.

PATIENTS AND METHODS

The cases of all of the patients with *H influenzae* and *S pneumoniae* bacteremia who were seen in Children's Hospital emergency services between July 1, 1977, and June 30, 1981, were reviewed. This period predates consistent presumptive treatment of patients at high risk for bacteremia. Information was collected by two observers from the initial visit, follow-up visits, and reports of telephone calls. The data included demographic information (age, race, sex, and payment status); information about this illness (temperature taken at home and in the emergency department, duration of fever, and medications taken at home); prior illnesses (complete medical record reviewed); laboratory tests performed (complete blood cell count; differential cell count; blood, urine, and cerebrospinal fluid latex fixation; chest roentgenogram; LP; urinalysis; and urine culture); diagnoses; and outcome. Clinical and laboratory criteria for each diagnosis were established prior to chart review. Five percent of the charts were reviewed by a third observer and the results were identical.

The written descriptions of the patients in the emergency services records were assessed and given a clinical score based on the appearance of the child: 1, a well-appearing child; 2, a mildly to moderately ill-appearing child; and 3, a very irritable or lethargic child, or a moderately irritable and lethargic child. The degree of irritability and lethargy was described in most of the records. If these precise words were not used, the provider's narrative was assessed as to the severity of the child's appearance (well, moderately ill, very ill).

Patients with blood cultures positive for *H influenzae* or *S pneumoniae* from the first visit were analyzed as one group initially.

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From the Division of Adolescent/Young Adult Medicine (Dr Woods), the Department of Medical Information (Dr Merola), and the Comprehensive Child Health Program (Dr Bithoney), Children's Hospital; the Department of Pediatrics, Harvard Medical School (Drs Woods, Bithoney, and Wise); The Joint Program in Neonatology, Brigham and Women's Hospital (Dr Wise); and Health Promotion Sciences, Massachussetts Department of Public Health (Dr Spivak), Boston, Mass.

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Reprint requests to Division of Adolescent Medicine, Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (Dr Woods).

Two patients with both organisms were deleted because the outcome could not be attributed primarily to either organism. Comparisons included ambulatory patients who were treated with antibiotics vs untreated patients, and patients who required hospital admission at subsequent visits vs those who were never admitted to the hospital.

Data analysis was performed using the SAS statistical package.[17] Fisher's Exact Test (two tailed) or χ^2 test was used for all categorical variables. For continuous variables, the appropriate t test was performed when comparison groups had equal variances (as assessed by the F test result), and an approximation of the t test was performed when comparison groups had unequal variances.[18] All results are stated as mean ± SD throughout this article. Of the variables with significant χ^2 and t tests, SAS's CATMOD logistic regression program was used to identify the best continuous and categorical predictors of the subsequent outcomes. The variables were grouped into three types of predictors for maximum efficiency: demographic variables, laboratory tests and results, and important initial variables (type of bacteremia, clinical score, initial hospital admission, and antibiotic treatment). Power calculations were performed using the tables developed by Cohen.[19] Odds ratios and the associated confidence intervals were calculated using Cornfield's method.[20]

Table 1.—Comparison of *Haemophilus influenzae* and *Streptococcus pneumonia*

	***H influenzae*, No. (%) (n = 167)**	***S pneumoniae*, No. (%) (n = 247)**	**P**
Demographics			
Race			
W	92 (55)	83 (34)	.0001
B	51 (31)	132 (53)	
Hispanic	18 (11)	21 (9)	
Insurance			
Insured	85 (56)	90 (41)	.0049
Medicaid	67 (44)	129 (59)	
Laboratory results*			
Hematocrit	0.33 ± 0.04	0.34 ± 0.04	.039
WBCs, $\times 10^9$/L	14.7 ± 8.1	19.3 ± 6.8	.0001
PMNs, $\times 10^9$/L	8000 ± 5500	11.6 ± 5.2	.0001
Positive LP culture†	69/98 (70)	7/93 (8)	<.0001
Clinical scale			
Well appearing (1)	12 (8)	47 (20)	.0001
Moderately ill (2)	65 (40)	156 (65)	
Very ill (3)	84 (52)	36 (15)	
Admitted to hospital at first visit	127 (76)	46 (19)	.0001

*WBCs indicates white blood cells; PMNs, polymorphonuclear leukocytes; and LP, lumbar puncture. Values are means ± SDs.

†One additional patient had meningitis with negative culture after treatment with antibiotics.

RESULTS

Overall Population

Information was obtained for 414 (99%) of 417 patients with *H influenzae* (n = 167) or *S pneumoniae* (n = 247) bacteremia. Patients had a mean age of 20.8 months (range, 1 to 228 months); 59% were male. Ninety-seven percent of the *H influenzae* bacteremia was type b, and 12% was resistant to ampicillin. The *S pneumoniae* included 22 different types, including one organism resistant to penicillin. The results of the initial visit are shown in Table 1. At the time of presentation in the emergency department, the patient's mean temperature was 39.6°C ± 1.0°C (range, 35.4°C to 41.6°C), and WBC count was $17.5 \pm 7.7 \times 10^9$/L (range, 0.05 to 72×10^9/L).

One hundred seventy-three patients (41.8%) were admitted to the hospital at the initial visit, and 241 patients (58.2%) were treated in the ambulatory setting. All patients with significant soft-tissue sources and/or immune suppression and 95% of all patients with chronic illnesses were admitted to the hospital at first presentation. More patients older than 36 months were immune suppressed when compared with younger patients (10.7% vs 0%, $P<.0001$). Patients older than 36 months had *H influenzae* bacteremia (60.7% vs 37.2%, $P = .0014$) and more soft-tissue sources at presentation (69.6% vs 38.8%, $P<.0001$) than younger patients. Follow-up information was available on all patients; 395 (95%) of 414 patients were seen for a follow-up visit for this illness at Children's Hospital. The other 19 patients had follow-up telephone calls (one with *H influenzae* and 18 with *S pneumoniae*) and were described by parents as well and afebrile.

H influenzae vs *S pneumoniae*

The initial diagnoses of the patients stratified by organism detected by blood culture are shown in Table 2. Patients with *H influenzae* were significantly more likely than patients with *S pneumoniae* to have a clear bacterial source evident at presentation (pneumonia, epiglottitis, buccal/facial/periorbital or other cellulitis, meningitis, abscess, wound infection, septic arthritis, or peritonitis) (145 [87%] of 167 patients vs 54 [22%] of 247 patients, $P<.0001$).

In comparison to patients with *S pneumoniae*, patients with *H influenzae* appeared more ill to clinicians; this is reflected by the greater number of laboratory tests performed, patients' significantly higher clinical score, more initial treatment with intramuscular or intravenous antibiotics before discharge home ($P = .0081$), and more frequent hospital admission at the first visit. Among ambulatory patients, there was no significant difference in the number of patients treated initially with some form of antibiotics with either organism.

The results of logistic regression analyses indicate that the most significant predictors of finding *H influenzae* on blood culture were the necessity for initial hospital admission ($P = .0001$), the higher clinical scale ($P = .017$), and the lower number of polymorphonuclear leukocytes ($P = .033$).

Ambulatory Treated vs Untreated Patients

The initial diagnoses of patients treated in the ambulatory setting before the blood culture results were available are given in Table 3. Of the patients who were not admitted to the hospital at the initial visit (ambulatory patients), 146 (60.6%) were treated with antibiotics and 95 (39.4%) were

Table 2.—Diagnoses at Presentation*

Diagnosis	*Haemophilus influenzae*, No. (n=167)	*Streptococcus pneumoniae*, No. (n=247)	*P*†
No serious soft-tissue source			
Otitis media	23	90	.0001
Viral syndrome	7	67	.0001
R/O bacteremia	3	35	<.0001
Fever	4	20	.015
Seizure	5	21	.024
Respiratory distress/asthma	5	4	NS
Pharyngitis	0	7	.028
Gastroenteritis	0	7	.028
Immune suppressed/defect	1	4	NS
Possible UTI/UTI	0	5	NS
Conjunctivitis	4	0	.026
Sinusitis	0	2	NS
Impetigo	0	1	NS
R/O meningitis	0	1	NS
Other	10	12	...
Serious soft-tissue sources			
Bacterial meningitis	68	7	.0001
Pneumonia (abnormal chest roentgenogram/clinical)	19	30	NS
Epiglottitis (abnormal findings on roentgenogram or from laryngoscopic studies)	25	0	<.0001
Buccal/facial cellulitis	13	4	.0039
Periorbital/orbital cellulitis	9	5	NS
Peritonitis	0	7	.045
Cellulitis	4	1	NS
Septic arthritis	5	0	.010
Subdural effusions	2	0	NS
Abscess	1	0	NS
Wound infection	1	0	NS
Pleural effusion	0	1	NS

*R/O indicates rule out; UTI, urinary tract infection; and NS, not significant.
†χ^2 or Fisher's Exact test.

Table 3.—Diagnoses of Ambulatory Treated and Untreated Groups*

Diagnosis	No Treatment, No. (%) (n=95)	Treatment, No. (%) (n=146)	*P*
Otitis media	0	99 (100)	<.0001
Viral syndrome	65 (90)	7 (10)	.0001
R/O bacteremia	10 (35)	19 (65)	NS
Pneumonia (abnormal chest roentgenogram/clinical)	0	27 (100)	<.0001
Fever	18 (95)	1 (5)	<.0001
Seizure	8 (47)	9 (53)	NS
Respiratory distress/asthma	3 (43)	4 (57)	NS
Pharyngitis	0	7 (100)	.044
Gastroenteritis	6 (86)	1 (14)	.011
Immune suppressed/defect	0	2 (100)	NS
Possible UTI/UTI	1 (25)	3 (75)	NS
Conjunctivitis	1 (33)	2 (66)	NS
Sinusitis	0	2 (100)	NS
Impetigo	0	1 (100)	NS

*R/O indicates rule out; UTI, urinary tract infection; and NS, not significant.

not treated. The two groups were comparable in demographic data, laboratory tests performed, and the results, as well as the types of organisms and clinical severity. The only significant difference was that treated patients had higher WBC counts ($19.5 \pm 6 \times 10^9$/L vs $17.6 \pm 6.4 \times 10^9$/L, $P = .026$). Most of the treated patients (93.2%) received penicillin and/or ampicillin and amoxicillin, and the remainder (6.8%) received sulfamethoxazole and trimethoprim, erythromycin and/or sulfisoxazole, or dicloxacillin. Patients with the diagnoses of pharyngitis, otitis media, pneumonia (proved clinically or by roentgenogram), sinusitis, abscess, or impetigo were all treated.

Patients treated at the initial visit were less likely to have otitis media develop (4.1% vs 19.0%, $P = .0002$) and more likely to be discharged from the hospital as a "well child" at subsequent visits (6.8% vs 0%, $P = .0071$) than untreated patients. In addition, patients who were treated initially had significantly fewer new foci of infection (Table 4), fewer positive blood cultures at follow-up visits, and fewer hospital admissions, despite the fact that treated patients had more potential bacterial diagnoses initially. When stratifying by organism, initial treatment of patients with *S pneumoniae* led to significantly fewer new foci (three [2.6%] vs nine [10.7%], $P = .030$), fewer subsequent positive blood cultures (one [0.8%] vs 15 [17.9%], $P < .0001$), and fewer subsequent hospital admissions ($P = .030$) than untreated patients. Treatment of patients with *H influenzae* did not significantly reduce the occurrence of new sources, subsequent positive blood cultures, or eventual hospital admission.

Patients with *H influenzae* were more likely to be admitted to the hospital subsequently than patients with *S pneumoniae*. Patients with higher clinical scores at the initial visit were more likely to be admitted at follow-up visits (1 [34.0%] vs 2 [33.3%] vs 3 [65.2%], $P = .011$). The best predictors of later hospital admission were *H influenzae* bacteremia ($P = .0001$), initial lack of treatment ($P = .0001$), and higher clinical scale ($P = .0040$).

Of the ambulatory patients, six (8.6%) of the 70 patients with initial normal results from LPs subsequently had

Table 4.—New Sources at Follow-up for Ambulatory Patients

Diagnosis	*Haemophilus influenzae* (n=40)	*Streptococcus pneumoniae* (n=201)	*P*	No Treatment (n=95)	Treatment (n=146)	*P*
Pneumonia (abnormal chest roentgenogram)	1	7	NS*	5	3	NS
Epiglottitis	2	0	.027	1	1	NS
Periorbital/orbital cellulitis	1	2	NS	3	0	NS
Meningitis	7	2	.0001	4	5	NS
Cellulitis	1	0	NS	1	0	NS
Septic arthritis and abscess	1	0	NS	0	1	NS
Adenitis	0	1	NS	1	0	NS
Total	**13**	**12**	.0001	**15**	**10**	.026
Subsequent positive blood culture, No. (%)	9 (22.5)	16 (8.0)	.0059	19 (20.0)	6 (4.1)	.0001
Subsequent hospital admission, No. (%)	31 (77.5)	61 (30.4)	.0001	50 (52.6)	42 (28.8)	.0002

*NS indicates not significant.

meningitis compared with three (1.8%) of 171 who did not have LPs (odds ratio = 5.2; 95% confidence interval, 1.1 to 23.6; *P* = .011). Patients with *H influenzae* bacteremia were more likely to have meningitis develop than those with *S pneumoniae* (seven [17.5%] of 40 vs two [0.1%] of 201; odds ratio = 21.1; 95% confidence interval 3.8 to 78.0; *P* = .0001) (Table 4). By logistic regression, the best predictors of meningitis at follow-up visits were *H influenzae* bacteremia (*P* = .0010), LP performed at the first visit (*P* = .0042), and a marginal association of higher clinical score (*P* = .067). Initial antibiotic treatment was not a significant predictor (*P* = .11) of subsequent meningitis, and there was sufficient power to detect a moderate or large effect.

COMMENT

The effect of anticipatory treatment of febrile children with antibiotics on the outcome of bacteremia is still controversial. The recent prospective study by Carroll et al[14] favors presumptive antibiotic treatment for febrile children, but only 10 of 96 patients examined were bacteremic. Jaffe et al[15] followed up 955 febrile children, yielding 27 with bacteremia, and they found that although the treated group did have improved clinical appearance and temperature at follow-up, no significant change in infectious morbidity in the treatment vs placebo groups was noted.[15] The authors acknowledged that the power of the comparison was low, because of the small numbers of bacteremic patients and subsequent new foci. Randomized prospective studies, however, must eliminate any diagnosis that requires initial treatment, and the patients must meet certain laboratory result criteria (eg, WBC count $>15 \times 10^9$/L) that may explain the low yield of bacteremic patients.[14,15] Klein[16] has suggested that antibiotics in potentially bacteremic patients may be justified. Further studies need to be performed to assess the risks and benefits of presumptive antibiotic treatment of large numbers of febrile children.

This study, which reviewed a large number (414) of patients with known *H influenzae* and *S pneumoniae* bacteremia, provided extensive information on the outcome of the patients and treatment plan. The patients treated and untreated in the ambulatory setting were comparable in all predictors, which supports the equivalence of the two treatment groups despite the lack of randomization because of the retrospective design. Five percent of the charts were independently reviewed by a third observer, which suggests observer bias had minimal effect on the variables collected. A retrospective case comparison (or case control) study can be more feasible and efficient than a prospective cohort study and can often yield more information when a disease incidence is low.[21] Retrospective, prospective randomized, and nonrandomized studies are not completely comparable, but each contributes important information for the understanding and treatment of potentially bacteremic patients.

Patients who were bacteremic with *H influenzae* were more likely to have a soft-tissue focus of infection and appear more ill at presentation than patients bacteremic with *S pneumoniae*. At follow-up visits, patients with *H influenzae* bacteremia were more likely to have development of serious soft-tissue sources, to be persistently bacteremic, and to require subsequent hospital admissions than patients with *S pneumoniae*. The increased rate of hospital admission may have been due, in part, to subsequent new foci, persistent fever/bacteremia, worse clinical appearance, and the greater likelihood that providers would admit a patient with *H influenzae* bacteremia to the hospital once the organism was known.

Ambulatory patients who were treated initially with antibiotics had fewer new serious foci of infections develop, had shorter duration of bacteremia (fewer subsequent positive blood cultures), and had fewer subsequent hospital admissions. They were more likely to be described as "well" at follow-up examinations than untreated patients. When stratifying by organism, there was a significant impact of treatment on all of these outcomes for patients with *S pneumoniae* but not for patients with *H influenzae*. Sullivan et al[22] indicated that patients with otitis media or pneumonia and patients with no recognizable source have similar low-grade bacteremias on quantitative blood cultures. If patients with pneumonia did, in fact, have higher-grade bacteremias, as Bell et al[23] suggested, one would expect that the treated patients in this study would have poorer outcomes. In addition, if patients did not comply with their medication regimens, one would expect no difference between the treatment groups. These biases would shift our results toward the null result, so that this would be a conservative estimate of the improved outcome of treated patients.

In agreement with Teele et al,[12] our data suggest that there is a significant association between the performance of an LP at initial presentation and the subsequent development of meningitis.

However, as in the report by Shapiro et al,[13] the relative risk of *H influenzae* bacteremia for the development of meningitis is much greater and the confidence interval is considerably farther from the null than the corresponding values for initial LP. The need for LPs and occurrence of subsequent meningitis may both reflect the severity of the patient's illness rather than indicate a cause and effect relationship.

Our study suggests that selected patients in a high-risk age group with a presumptive diagnosis of bacteremia may benefit from treatment with antibiotics to prevent a new serious soft-tissue infection, persistent bacteremia, and subsequent admission to the hospital. The greatest impact of treatment was on patients with *S pneumoniae*. Treating selective high-risk ambulatory patients with presumptive bacteremia after appropriate evaluation may reduce the patient's morbidity and cost of hospitalization; however, careful follow-up and reevaluation is essential, since treated and untreated patients can still develop serious soft-tissue infections.

Paula George, MD, assisted with data collection and gave helpful comments throughout the study. S. Jean Emans, MD, and Donald Goldmann, MD, provided helpful comments; the bacteriology laboratory of The Children's Hospital assisted in identifying cases; and Matthew Wehmas provided initial programming assistance.

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Book Review

Pediatric and Adolescent Gynecology, 3rd edition, by S. Jean Herriot Emans and Donald Peter Goldstein, 621 pp, with illus, $46.50, Boston, Mass, Little Brown & Co Inc, 1990.

Adolescent Sexuality and Gynecology, by Donald E. Greydanus and Robert B. Shearin, 313 pp, with illus, $27.50, Philadelphia, Pa, Lea & Febiger, 1990.

Both of these books supply essential information about adolescent gynecology and sexuality. *Pediatric and Adolescent Gynecology* is the third edition of a text last revised in 1982. During the past 8 years, much has changed in the field of adolescent gynecology. There are new diseases, new contraceptives, and new treatment regimens. This edition admirably incorporates this new knowledge in every chapter. I am particularly impressed that the references include pertinent journal articles published as recently as early 1990. A chapter on human immunodeficiency virus and human papillomavirus infection has been added. Legal aspects of pediatric and adolescent gynecology are also discussed. This edition is about 250 pages longer than the second. The chapters on sexual abuse, delayed puberty, and painful gynecologic disorders, in particular, are far more comprehensive than in the second edition. Although some of the figures and tables have not changed, an excellent color plate has been added that includes 18 photos of external genitalia.

Adolescent Sexuality and Gynecology provides a good general overview of adolescent gynecology. It is more concise and "readable," but the text and references are not as comprehensive as Emans and Goldstein's text. Emans and Goldstein's text also discusses gynecologic problems in the preadolescent girl that are not addressed by Greydanus and Shearin's text.

Both of these books discuss examination techniques, breast disorders, normal and abnormal puberty, menstrual dysfunction, genital infections, sexual abuse, and sexuality education. Greydanus and Shearin's text includes a chapter on adolescent nutrition and substance abuse. Emans and Goldstein's text provides a better discussion on contraception than does Greydanus and Shearin's text. It discusses newer contraceptive methods and includes a more detailed discussion on treating the patient taking oral contraceptives.

Both of these books would be a useful addition to any pediatrician's personal library.

MARY E. RIMSZA, MD
Maricopa Medical Center
Department of Pediatrics
PO Box 5099
Phoenix, AZ 85010

Total and Differential Leukocyte Counts in Clinically Well Children

Information or Misinformation?

Virginia A. Moyer, MD, MPH, Richard M. Grimes, PhD

• To determine whether the total and differential leukocyte count is of value as a case-finding test, we applied the evaluation criteria developed by the US Preventive Services Task Force. The criteria comprise review of the current burden of suffering of the disease to be prevented, the attributes of the intervention to be used, and the quality of the evidence available. A literature search revealed no evidence in the form of data from patients, so a chart review of all complete blood cell counts ordered during a 1-year period by one group of pediatricians was undertaken. At least one value outside of published normal ranges was found on 74.7% of the tests performed on clinically well children. No unsuspected illness was discovered as a result of an abnormal total and differential leukocyte count.

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The US Preventive Services Task Force has evaluated screening and case-finding interventions for a number of conditions with the use of rules of evidence developed in cooperation with the Canadian task force.[1,2] Unfortunately, little of its activity has focused on the health supervision needs of children.

The total and differential leukocyte count, included in a complete blood cell (CBC) count, is often used as a case-finding test in both adult and pediatric patients. In 1983, Rich et al[3] noted the frequent use of the test as a case-finding tool in their adult medicine clinic and retrospectively evaluated its use. No unsuspected disease was diagnosed with the use of this test in their population. Wesson et al[4] reviewed the outcomes of differential leukocyte counts on 122 clinically healthy midshipmen who were being screened for submarine duty. None of the abnormalities that were reported represented unsuspected disease. Both groups concluded that the test was not useful in screening adult patients.

A MEDLINE search of the literature since 1966, review of major pediatric and pediatric hematology texts, and a hand search of references from related articles found in the search revealed no published evidence other than expert opinion regarding case finding with total and differential leukocyte counts in the pediatric population.

Despite the fact that this test is not included in the health supervision guidelines of the American Academy of Pediatrics, Elk Grove Village, Ill, the authors believe that it is widely used as a part of health supervision in pediatric patients. The purpose of this study was to provide clinical evidence on the usefulness of the total and differential leukocyte count in pediatric health supervision and to evaluate the test with the use of the method promulgated by the US Preventive Services Task Force. As this study was designed to evaluate only the total and differential leukocyte count as a case-finding test in pediatrics, the other information obtained in a CBC count will not be discussed here.

PATIENTS AND METHODS

Clinical Study

The Kelsey-Seybold Clinic in Houston, Tex, is a large private group practice that serves about 200 000 health maintenance organization and fee-for-service patients at 12 sites. The patient population is racially and ethnically mixed, but includes essentially no indigent patients.

Computer reports of all CBC counts ordered by the pediatricians at one clinic site for the 12-month period from December 1985 to November 1986 were generated. Twelve-month reports were complete for three pediatricians. Charts were retrieved for these patients, and the child's condition on the day of the test was recorded as "well" or "ill." Children who came in for well-child care, who had no medical complaints, and whose diagnosis was recorded as "normal examination," "well child," "normal checkup," and so forth, were classified as clinically well. The children whose diagnosis on that day included any medical problem were classified as not clinically well. Only values obtained on children who were asymptomatic and had normal physical examination results recorded were considered in this study.

Total and differential leukocyte counts were classified as abnormal or normal based on the presence or absence of an asterisk that was automatically printed on the laboratory report next to the total leukocyte count or next to the percentage of any white blood cell type in the differential cell count that fell outside of the age-based normal ranges used by the laboratory. The ranges were taken from the 1977 edition of the pediatric textbook of Rudolph[5] and are attributed in the text to Albritton[6] (1952).

If the results were flagged as abnormal on the laboratory report slip, the chart was examined for evidence of acknowledgment by the ordering physician. Such evidence included mention of the abnormality in the progress notes, a circle or exclamation point marking the abnormal value, or a note written on the laboratory report slip itself. Repeated CBC counts that were performed for any reason were recorded, and all charts were evaluated for occurrence of symptoms or disease and length of follow-up since the date of the test.

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From the Kelsey-Seybold Clinic (Dr Moyer) and the Department of Pediatrics, Division of Community and General Pediatrics, School of Medicine (Dr Moyer) and the School of Public Health (Dr Grimes), University of Texas Health Science Center at Houston. Dr Moyer is now with the University of Texas Health Science Center at Houston.

Reprint requests to Department of Pediatrics, University of Texas Health Science Center, 6655 Travis, Suite 570, Houston, TX 77030 (Dr Moyer).

The charts were reviewed more than 6 months after the date of the last CBC count performed, in a population that was, to some degree, "captive" because of health maintenance organization membership. It has therefore been assumed that adverse events occurring within a few months of the test would have been reflected in the chart. It was not possible to contact patients to obtain information for this study.

This study was approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston, and by the administration of the Kelsey-Seybold Clinic.

US Task Force Criteria

The US Preventive Services Task Force criteria provide widely accepted standards for evaluating a case-finding test. The criteria for evaluating screening tests comprise (1) the burden of suffering on the individual and on society imposed by the condition to be prevented, (2) the attributes of the screening test itself, and (3) the quality of the evidence obtained in support of the intervention. Regarding the condition, it should be an important health problem ("burden of suffering"), there should be an accepted treatment available that is more effective when applied earlier, and there must be a reasonable period in the natural history of the condition during which symptoms are not yet present or obvious. Regarding the test, it must be simple to perform, with good sensitivity and reasonable specificity, and the cost of case finding (including follow-up testing for definitive diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole. Regarding the quality of evidence, the Task Force ranks randomized trials as the best evidence, nonrandomized clinical studies as next best, and expert opinion as the least supportive evidence.

After weighing the information on the condition, the test, and the evidence, a recommendation is made as to whether the intervention belongs in the periodic health examination. The evaluation criteria are summarized in Table 1.

RESULTS

Of the total of 778 CBC counts ordered during the 1-year period, 387 (49.7%) were drawn from children who were noted to be asymptomatic and clinically well. These children were 51% female and ranged in age from 1 month to 17 years, with most being in the preschool age group.

At least one asterisk was present, indicating that a part of the total or differential leukocyte count was outside of the laboratory's normal range, on 289 (74.7%) of these. Only 13 (4.5%) of these abnormal values were acknowledged by the ordering physician. A repeat CBC count was performed at a later date, usually during an acute illness, for 83 (21.4%) of the 387 children.

Length of follow-up ranged from none—that is, the patient's last visit was on the date of the test—to 21 months, with a mean of 7.8 months. No new illness was discovered as a result of an abnormal total or differential leukocyte count performed on a clinically well child. Results regarding evidence can be summarized as follows: of 778 CBC counts ordered, 387 were ordered for clinically well children. Of these, 98 (25.3%) were within normal limits and 289 (74.7%) were outside published normal limits. None of these clinically well children developed illness related to a CBC abnormality.

In this study, 38 (9.8%) of the 387 clinically well patients had absolute neutrophil counts of less than 1.5×10^9/L. Seven of these were acknowledged, of whom four had repeated tests ordered. Another 12 patients had CBC counts done at later dates for other reasons. Of all 16 repeated CBC counts, 12 (75%) reverted to normal. The remaining four (1% of all the well children) continued to show moderately decreased absolute counts (1.0 to 1.5×10^9/L) but remained clinically healthy 11 to 18 months later. They had no further CBC counts or evaluations performed.

Fourteen (3.6%) clinically well patients initially showed absolute eosinophil counts greater than 0.7×10^9/L, of which one was acknowledged but not followed up. The five patients who had CBC counts performed at later dates all showed resolution of their eosinophilia. No patient experienced new disease associated with eosinophilia during the period of follow-up.

COMMENT

The number of children with occult disease that could be picked up with the use of this test depended on the prevalence in the community of the disease for which one was screening, and the test could only be evaluated with reference to the specific condition or conditions being sought. Because the leukocyte is a reactive tissue cell, hundreds of diseases are associated with abnormal leukocyte counts, but only conditions in which the abnormality in the leukocyte count occurs before clinical presentation are subject to screening with the use of this test.

The pediatricians at all 12 clinic sites were informally surveyed regarding their use of this test. More than half stated that they routinely ordered CBC counts as a part of well-child care. When asked, those who used the test cited "screening" and "completeness" as the reasons for performing this test at well-child examinations. One pediatrician specifically recalled that this practice was taught during residency.

When asked what diseases or conditions might be detected with the use of the total and differential leukocyte count included in the CBC count, the pediatricians who routinely used the test listed leukemia, neutropenia, and eosinophilia. Several also stated that the finding of any abnormality would provide useful information. These three specific conditions were examined in relation to the criteria in the "condition" section of Table 1. The results relating to specific conditions are summarized in Table 2. The issue of finding "any abnormality" to be useful information is discussed below.

Leukemia has an annual incidence of 42 per million white children and 24 per million black children in the United States. Although rare, it is a severe disease with a treatment that is probably more effective when applied earlier in its course. It appears, however, that the presymptomatic phase is short, so there would be only a small window of time in which screening might be useful.

Table 1.—Evaluation Criteria

Criteria
Condition
Importance (burden of suffering)
Effective early intervention
Presymptomatic period
Test
Simple, sensitive, specific
Reasonable cost
Evidence
Randomized trials (I)
Nonrandomized studies (II)
Expert opinion (III)

Table 2.—Results for Conditions*

Condition	Burden/ Importance	Early Intervention	Presymptomatic Period
Leukemia	+	+/−	−
Neutropenia	−	−	−
Eosinophilia	+	−	−

*Plus sign indicates that the criterion was met; minus sign, the criterion was not met.

Table 3.—Use of Sensitivity, Specificity, and Prevalence to Calculate Expected Ratio of False Positives to True Positives*

	Diseased	Not Diseased	Total
Test positive	95	4995	5090
Test negative	5	94 905	94 910
Total	100	99 900	100 000

*Sensitivity = 95/(95 + 5) = 95%. Specificity = 94 905/(94 905 + 4995) = 95%. Prevalence = 100/(100 + 99 900) = 1/1000. Positive predictive value = 95/(95 + 4995) = 1.9%. Ratio of false positives to true positives = 4995/95 = 53.

Neutropenia and eosinophilia are not themselves diseases, but are conditions defined by laboratory values. Isolated primary neutropenia is extremely rare, and generalized bone marrow failure is unlikely to be asymptomatic, even in its early stages. Eosinophilia is associated with a large number of disorders, but the relationship of eosinophilia with most such disorders is not consistent enough for eosinophilia to be used as a predictor. Parasitic tissue infestations, such as trichinosis or visceral larva migrans, do demonstrate consistently high eosinophil counts, but lack efficacious therapy to justify screening.

The CBC count is usually an automated count of the red and white blood cells and platelets and a measurement of the red blood cell indexes in a sample of peripheral blood. It has been demonstrated that from 50% to 75% of the variance in leukocyte differential counts is not attributable to disease, but to variability in sampling (in the patient and in the specimen), in counting, and in observers.[7] This attribute of the test severely limits its potential usefulness in screening and case finding.

There are both monetary and nonmonetary costs associated with the use of screening tests.[8] The cost should be justified in terms of the benefits gained. Unlike the rest of the CBC count, the differential leukocyte count must be performed manually in many laboratories. Even where automated differential counting is available, 30% to 40% of the counts must be repeated manually because of abnormalities suspected.[7] As Shapiro et al[9] have shown, the potential for cost savings by reduction in laboratory use is greatest for labor-intensive tests, such as the leukocyte differential count. The additional costs of follow-up visits and follow-up tests must also be considered.

Suggesting to patients or parents that there may be something wrong and that more testing is needed may carry a psychological cost, the dollar value of which cannot be estimated.[10] Finally, there is the ever-present specter of legal liability that is generated when a laboratory value is flagged as abnormal and then ignored. Even if ignoring the value was medically entirely appropriate, it may be hard to defend to a lay jury in the presence of a patient with an adverse outcome.

Expert opinion and committees, such as the American Academy of Pediatrics' committee that developed the Guidelines for Health Supervision, do not mention the use of this test in case finding.[11] It is also not recommended in the adult literature.[12]

The approach of routine care has been to examine the patient in a general way (by physical, behavioral, and laboratory means) to confirm wellness rather than rule out specific illness. The availability of automated equipment that can generate large quantities of information with apparently minimal effort may be one of the reasons for ordering a test like the CBC count, which contains at least 14 pieces of information, rather than a simple hematocrit, or even a CBC count without a differential cell count. The particular examinations to be performed have been developed through habit and custom and have not often been critically analyzed as to utility.

We are accustomed to using the total and differential leukocyte count in diagnosing the conditions of sick patients: why not use the same information in well patients? It is precisely because sick patients probably have something wrong with them, and well patients probably do not, that this intuitive logic fails. When the prevalence of disease is low, even sensitive and specific tests have many more false-positive than true-positive results. The pretest likelihood that a clinically well child has any particular disorder, or any disorder at all, is low. Unless a test is nearly 100% sensitive for a disorder, it is not useful in screening. But if that same test is not also nearly 100% specific, the number of false alarms leading to unnecessary follow-up testing and/or intervention will be high. For example, if a patient has a 1 in 1000 chance of having a disease, and the test is 95% sensitive and 95% specific, the predictive value of a positive test will be 1.9%. That is, for every patient with a correctly identified disease, 53 patients without disease will need follow-up testing to demonstrate that they do not have disease (Table 3).

If the abnormal value is ignored because disease is so unlikely, then there is not any point in getting the test in the first place. In this study, only 13 of 289 values that fell outside of the age-based normal ranges were acknowledged. In a similar study of case finding in adults by Rich et al,[3] physicians failed to note 86% of the abnormalities of case-finding differential leukocyte counts, and the same appears to apply to abnormal results of chemical screening batteries in adult patients.[13]

The clinical relevance of published normal ranges is called into question by our data. The number of cases in which the total or differential white blood cell count was marked as abnormal was strikingly high. In this study, 74.7% fell outside the published, age-based normal ranges that were used by the laboratory. The same table of normal values is found in the 1987 editions of the textbook of Rudolph[14] (for age, >1 month) and in the pediatric hematology textbook of Nathan and Oski.[15] That so many children would have abnormal blood cell counts does not make clinical sense, and is likely to be one of the reasons that so many of these results were ignored by the ordering physician.[16]

There are several possible reasons for

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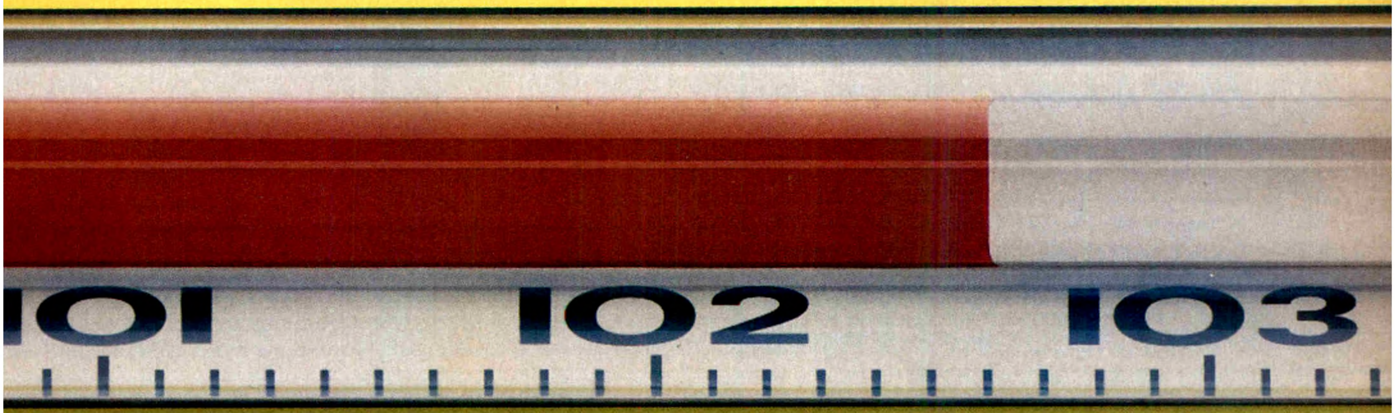

Superior reduction for fevers over 102.5°F

Proven efficacy
For reducing children's temperatures over 102.5°F, ibuprofen 10 mg/kg was proven more effective than acetaminophen 10 mg/kg.[1]

Longer duration of action for fevers over 102.5°F
For duration of fever relief, ibuprofen 10 mg/kg was proven more effective than acetaminophen 10 mg/kg —relief lasted up to 8 hours.[1,2]

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Please see brief summary of Prescribing Information on the next page.

References:
1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

Superior reduction for fevers over 102.5°F

PediaProfen™

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—
orange, berry-vanilla flavored

Bottles of 4 oz (120 ml) .... NDC 0045-0469-04
Bottles of 16 oz (480 ml) .... NDC 0045-0469-16

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Immune Complexes in Pediatric Human Immunodeficiency Virus Infection

Maadhava Ellaurie, MD; Theresa Calvelli, PhD; Arye Rubinstein, MD

• Circulating immune complexes (CIC) were analyzed in a cohort of 30 children

Laboratory Methods

Immunoglobulin and C3 levels were de-

utes. The precipitated CIC were resuspended in 2 mL of 2% polyethylene glycol in

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gens and thus escape detection in routine serum antibody assays.

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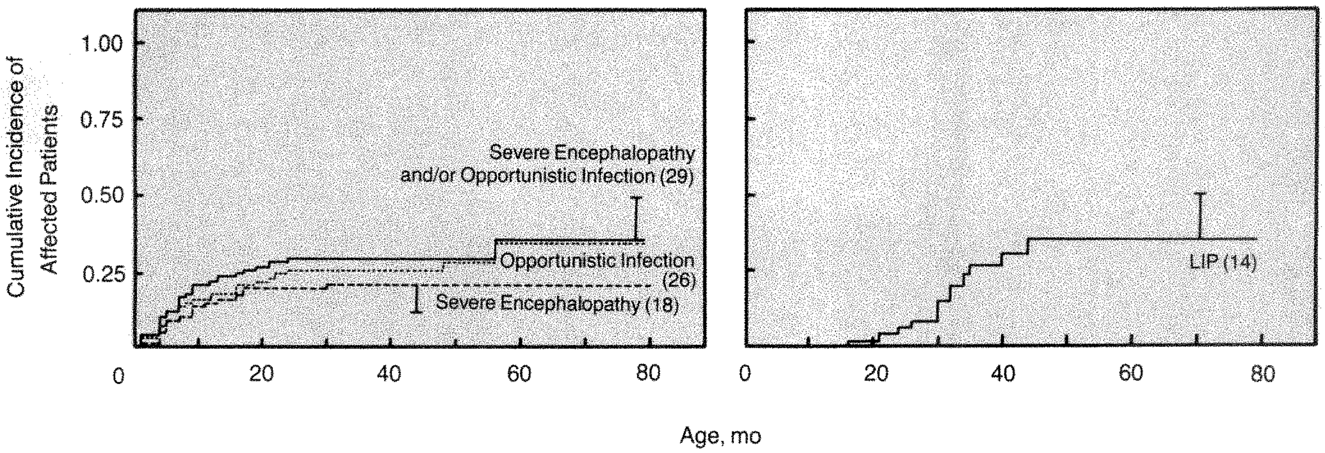

Fig 2.—Left, Progression curves to opportunistic infections (26 patients) and severe encephalopathy (18 patients) in either one or both (29 patients). Right, Progression curves to lymphoid interstitial pneumonitis (LIP) (14 patients). Vertical bars represent the 95% confidence interval.

amination. The origin of maternal infection, including drug addiction or geographic location, did not influence the

Table 2.—Variation of Neurological Score During the Course of the Disease

Initial	Neurological Score at the End of Follow-up*

[redacted]

[redacted]

dition, the expression of clinical symptoms and biological abnormalities does not follow a bimodal distribution in the adult population. Another hypothesis could be that a very early transmission of the virus during fetal life, or a transmission of HIV-1 together with other microorganisms, interferes with the

early occurring and severe impairment might suffer from an early subacute insult. This insult might induce a gross parenchymal destruction, because of cytotoxic factors released by massively infected monocytes or microglial cells. Subsequently, chronic lesions would persist. In patients with a slowly pro-

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10. Epstein LG, Boucher CAB, Morrisson SH, et al. Persistent human immunodeficiency virus type I antigenemia in children correlates with disease progression. *Pediatrics.* 1988;82:919-924.

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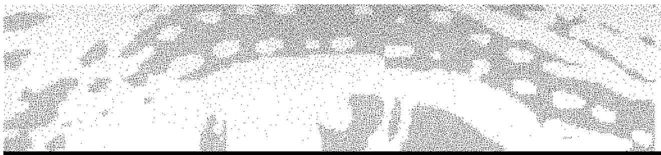

Guarding the

[redacted]

Special Contribution

Diagnostic Guidelines for Kawasaki Disease

American Heart Association Committee on
Rheumatic Fever, Endocarditis, and Kawasaki Disease

Kawasaki disease, or mucocutaneous lymph node syndrome, is a disease of unknown origin that most frequently (80% of the time) affects infants and children under 5 years of age. Accurate diagnosis and early therapeutic interventions, such as aspirin and intravenous γ-globulin can decrease the approximately 20% risk of developing coronary artery abnormalities. A specific diagnostic test does not exist. Thus, diagnosis of Kawasaki disease is based on characteristic clinical signs and symptoms, which are classified as *principal clinical findings* and *other significant findings.* The male-to-female ratio among patients with Kawasaki disease is 1.5:1. Children of nearly all racial backgrounds are affected. Recurrences and cases in siblings are seen only occasionally.

PRINCIPAL CLINICAL FINDINGS

These include *fever persisting at least 5 days* and the following other principal features: (1) changes in peripheral extremities, including acute, ie, erythema and edema of hands and feet, and convalescent, ie, membranous desquamation of fingertips; (2) polymorphous exanthem; (3) bilateral, painless bulbar conjunctival injection without exudate; (4) changes in lips and oral cavity, such as erythema and cracking of lips, strawberry tongue, and diffuse injection of oral and pharyngeal mucosae; and (5) acute, nonpurulent cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral.

Fever and at least four of the remaining five features should be present to establish the diagnosis of Kawasaki disease. However, patients with fever and fewer than four principal symptoms can be diagnosed as having Kawasaki disease when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography. Other diagnoses should be excluded. The physician should be aware that some children with illnesses not fulfilling these criteria have developed coronary artery aneurysms.

OTHER SIGNIFICANT CLINICAL AND LABORATORY FINDINGS

Cardiovascular. — Symptoms include the following: on auscultation, gallop rhythm or distant heart sounds; electrocardiogram changes (arrhythmias, abnormal Q waves, prolonged PR and/or QT intervals, occasionally low voltage, or ST-T wave changes); chest roentgenographic abnormalities (cardiomegaly); echocardiographic changes (pericardial effusion, coronary aneurysms, or decreased contractility); mitral and/or aortic valvular insufficiency; and rarely, aneurysms of peripheral arteries (eg, axillary), angina pectoris, or myocardial infarction.

Gastrointestinal. — Symptoms include diarrhea, vomiting, abdominal pain, hydrops of the gall bladder, paralytic ileus, mild jaundice, and mild increase of serum transaminase levels.

Blood. — Symptoms include increased erythrocyte sedimentation rate, leukocytosis with left shift, positive C-reactive protein, hypoalbuminemia, and mild anemia in acute phase of illness (thrombocytosis in subacute phase).

Urine. — Symptoms include sterile pyuria of urethral origin and occasional proteinuria.

Skin. — Symptoms include perineal rash and desquamation in subacute phase and transverse furrows of fingernails (Beau's lines) during convalescence.

Respiratory. — Symptoms include cough, rhinorrhea, and pulmonary infiltrate.

Joint. — Symptoms include arthralgia and arthritis.

Neurological. — Symptoms include mononuclear pleocytosis in cerebrospinal fluid, striking irritability, and rarely, facial palsy.

The Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease.—Adnan S. Dajani, MD (chairman); Alan L. Bisno, MD; Kyung J. Chung, MD; David T. Durack, MD, DPhil; Michael A. Gerber, MD; Edward L. Kaplan, MD; H. Dean Millard, DDS, MS; Martin F. Randolph, MD; Stanford T. Shulman, MD; Kathryn A. Taubert, PhD; Chatrchai Watanakunakorn, MD.

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Prepared by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association's Council on Cardiovascular Disease in the Young.

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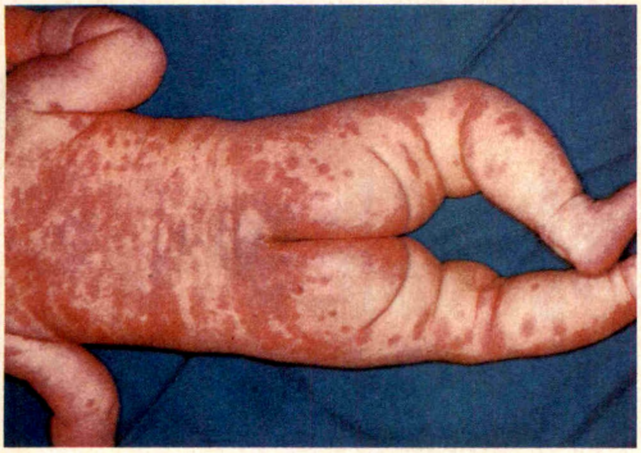
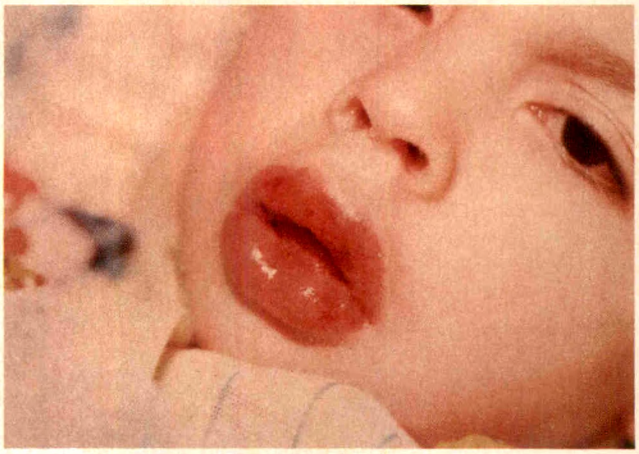
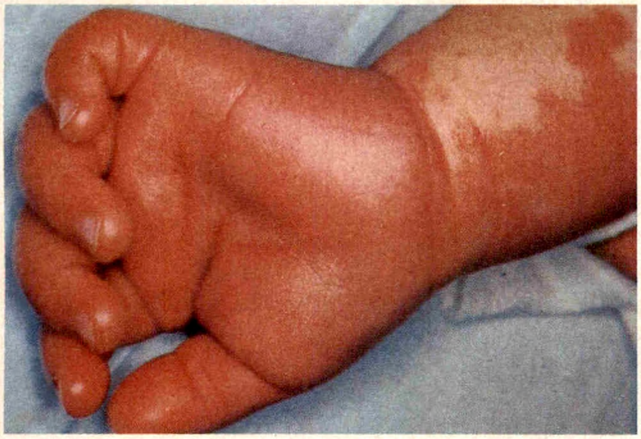
Reprint requests to American Heart Association, 7320 Greenville Ave, Dallas, TX 75231 (Kathryn A. Taubert, PhD).



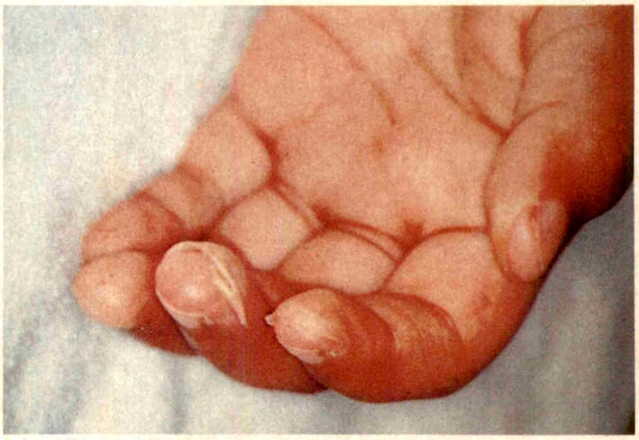
Rash of Kawasaki disease in a 7-month-old boy on the fourth day of illness.



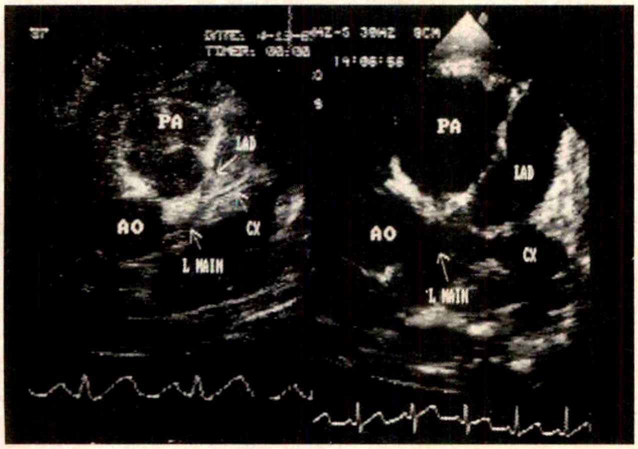
Conjunctival injection, lip edema, and erythema in a 2-year-old boy on the sixth day of illness.



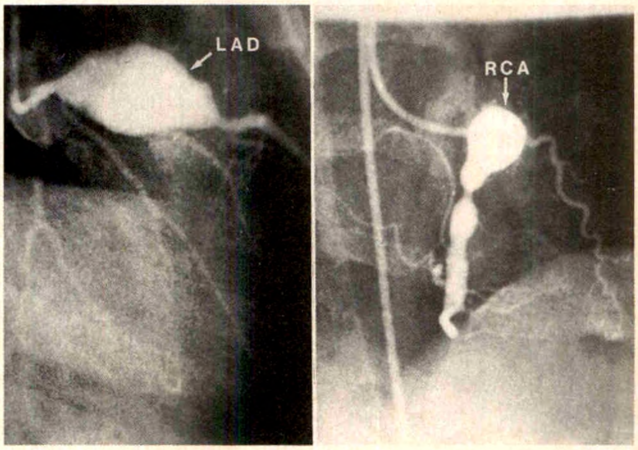
Erythematous and edematous hand of a 1.5-year-old girl on the sixth day of illness.



Periungual desquamation in a 3-year-old on the 12th day of illness.



Two-dimensional echocardiogram. AO indicates aorta; PA, pulmonary artery; LAD, left anterior descending coronary; CX, circumflex coronary; and L Main, left main coronary.



Coronary angiogram demonstrating hugely dilated left anterior descending (LAD) artery with obstruction and very dilated right coronary artery (RCA) with an area of severe narrowing, in a 6-year-old boy.

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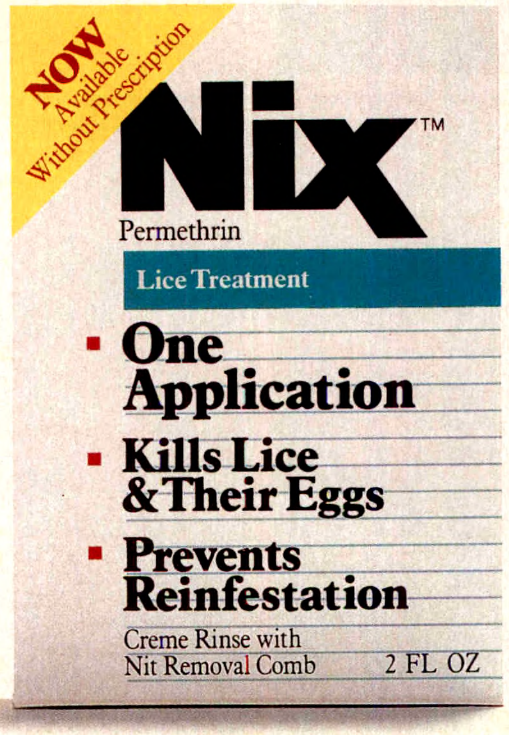

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1. Brandenburg K, Deinard AS, DiNapoli J, Englender SJ, Orthoefer J, Wagner D. 1% permethrin cream rinse vs 1% lindane shampoo in treating pediculosis capitis. *Am J Dis Child.* 1986;140:894-896. 2. Data on file, Burroughs Wellcome Co., 1990.

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Articles

Childhood Deaths From Toy Balloons

C. Anthony Ryan, MB, MRCP, FRCPC; Wadieh Yacoub, MB BCh, MSc;
Tom Paton, MB ChB, MPH, FRCPC; Denise Avard, PhD

- **We describe four children who died of suffocation by rubber balloons in Canada between 1983 and 1988. In the United States, at least 121 children have died in a similar manner in the 15 years between 1973 and 1988 according to a report by the US Consumer Product Safety Commission. Although the highest mortality occurred among infants, 30 (25%) of the 121 deaths occurred in children 6 years of age or older. Balloons account for 43% of the approximately 15 childhood deaths related to children's products that are documented each year by the Consumer Product Safety Commission. Toy rubber balloons are thus the leading cause of pediatric choking deaths from children's products. Preventive efforts should be directed toward a ban on this type of balloon and the development of safer alternatives. Meanwhile, public information campaigns should alert parents, physicians, and policymakers to the dangers of toy rubber balloons.**

(*AJDC*. 1990;144:1221-1224)

Foreign body aspiration with subsequent airway obstruction typically occurs in children between ages 6 months and 5 years.[1] It is approximately twice as common in boys as in girls.[2] Although the majority of accidental deaths by choking in childhood are due to inhalation of food objects such as hot dogs, candies, nuts, and grapes,[3,4] deaths also occur from common household and nonfood objects and toys, including toy rubber balloons.

We report the deaths caused by choking on toy rubber balloons of four children occurring in the last 5 years in Canada. In addition, the epidemiology of rubber balloon-related deaths in children in the United States is presented. The management of acute airway obstruction by foreign bodies is reviewed and guidelines to prevent these tragic deaths are suggested.

METHODS

The first patient described below was referred to the University of Alberta Hospitals, Edmonton, while three other deaths from rubber balloons were traced by contacting all the chief coroners in Canada. The present international coding system of deaths (ICD 9E) has two subclassifications of deaths from choking: airway obstruction by food and nonfood objects. Deaths from toy balloons are contained in the latter category; however, under the present classification system they cannot easily be retrieved. Therefore, the Canadian cases were traced from the chief coroner's recall of specific events.

The epidemiology of childhood choking deaths from balloons in the United States was acquired from data provided by the National Injury Information Clearinghouse of the US Consumer Product Safety Commission (CPSC). The CPSC was created in 1973 "to collect, investigate, analyze, and disseminate injury data and information relating to causes and prevention of death, injury, and illness associated with consumer products."[5] Product-associated deaths, extracted nationwide from both paid and voluntary reporting of death certificates, are a major resource. Because it relies on voluntary and paid information and does not have a database based on statistical sampling, the total number of deaths collected by the CPSC is always an underestimate of the true number of product-related deaths.

PATIENT REPORTS

PATIENT 1.—According to his mother, a 9-year-old boy had a habit of picking up little objects and putting them into his mouth. In November 1988, he found an uninflated rubber balloon in the school playground that he put into his mouth to chew on. When a classmate told a joke, the boy laughed and threw his head back. He immediately choked on the balloon and fell to the ground. A member of the teaching staff attempted the Heimlich maneuver without success. The boy was brought to the nearest hospital within 5 minutes of the event where he was found to be cyanosed, not responding to painful stimuli, with a heart rate of 120 beats per minute, and grunting respirations of 12/min. He was intubated but could not be ventilated because of obstruction distal to the endotracheal tube. A tracheostomy was performed during which he had a respiratory arrest and subsequently a cardiac arrest. An intact rubber balloon was withdrawn through the tracheostomy wound. However, it took 20 minutes of cardiopulmonary resuscitation to establish a pulse. He was transported to a tertiary care pediatric intensive care unit where an electroencephalogram showed severe disturbance of cerebral function consistent with hypoxic encephalopathy. Despite supportive therapy, his condition continued to deteriorate and he was declared brain dead 48 hours later.

PATIENT 2.—In August 1984, a 2 3/4-year-old girl was noted by her sibling to be playing with a deflated toy rubber balloon in her mouth. When her mother manually attempted to remove it, the child became limp and unresponsive. She was immediately transferred to a nearby hospital and was given cardiopulmonary resuscitation. However, all attempts at resuscitation were unsuccessful. At autopsy, a collapsed rubber balloon was found lodged deep within the trachea with the tip extending into the right main stem bronchus.

PATIENT 3.—In November 1982, a 4-year-old girl received an uninflated rubber balloon at a classroom birthday party. During recess the child approached the school yard supervisors seeking assistance and pointing toward her mouth with her finger. Her lips were blue. Neither of the supervisors was aware of the birthday party or the balloons. One of the supervisors probed inside her mouth with her finger in an effort to establish the source of the child's discomfort. Nothing was located orally and the child was turned upside down and slapped on the back in an effort to dislodge what was felt to be an obstruction in

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Accepted for publication March 26, 1990.

From the Pediatric Intensive Care Unit (Dr Ryan), University of Alberta (Canada) Hospitals, Edmonton; the Department of Pediatrics, University of Alberta, Edmonton (Drs Ryan and Patton); The Edmonton Board of Health (Drs Yacoub and Paton); and The Canadian Institute of Child Health, Ottawa, Ontario (Dr Avard).

Read before the Pediatric Critical Care Colloquium, Santa Monica, Calif, October 28, 1989.

Reprint requests to Department of Pediatrics, 2C300 Walter Mackenzie Health Sciences Centre, Edmonton, Alberta, Canada T6G 2R7 (Dr Ryan).

the child's throat. The child became limp and unconscious. Repeated Heimlich maneuvers, performed by the school staff and paramedics, were unsuccessful. The child was taken to the nearest hospital where a cricothyroidotomy was performed. However, the child could not be ventilated through the cricothyroidotomy and further attempts at resuscitation failed. At autopsy, a deflated rubber balloon was removed from below the larynx with a Magill's forceps.

PATIENT 4.—In June 1986, during a family celebration, a 2-year-old boy bit into an inflated rubber balloon, puncturing the balloon. He immediately started gasping and choking. The parents, realizing he may have aspirated a piece of the balloon, began cardiopulmonary resuscitation and took the child by car to the nearest hospital, approximately 1 hour away. At the same time, an ambulance with a physician on board was dispatched from the hospital and met them halfway. The child was intubated but was difficult to ventilate. On arrival at the hospital, a bronchoscopy was performed revealing a small piece of balloon at the level of the carina obstructing the main bronchi. Once the balloon piece was removed, ventilation became quite easy. However, 90 minutes had elapsed from the time the child obstructed and the removal of the balloon; at this stage, the child was declared brain dead. An autopsy was not performed.

US EPIDEMIOLOGY

The CPSC has established that at least 121 children have died by choking on toy balloons in the 15 years between 1973 and 1988 (Fig 1); the age distribution of the children who died is illustrated in Fig 2. Although the highest mortality occurred among infants, 30 (25%) of the 121 deaths involved children aged 6 years or older.

Of the approximately 150 children who die each year in the United States by choking on nonfood objects, 90% die from choking on objects such as nails, bolts, and tacks, and some are said to result from choking on mucus and phlegm. Only about 15 (10%) of the 150 nonfood choking deaths annually are related to children's products. However, 43% of the latter deaths are due to toy balloons, 22% occur when children choke on small balls, 5% are due to marbles, while the remainder (30%) occur from a variety of miscellaneous children's products.[6]

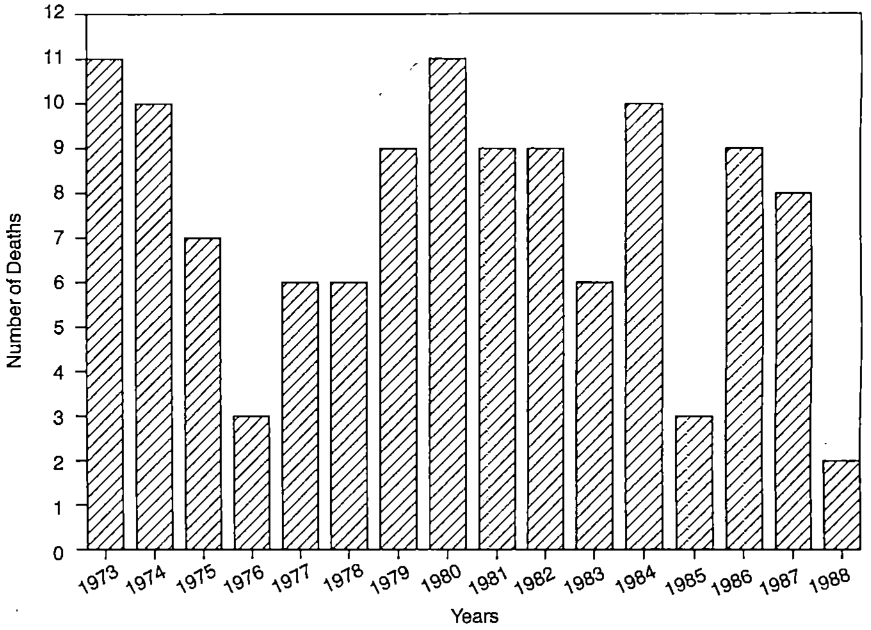

Fig 1.—Distribution by year of 121 childhood deaths from choking on toy rubber balloons or balloon pieces documented by the Consumer Product Safety Commission between 1973 and 1988.

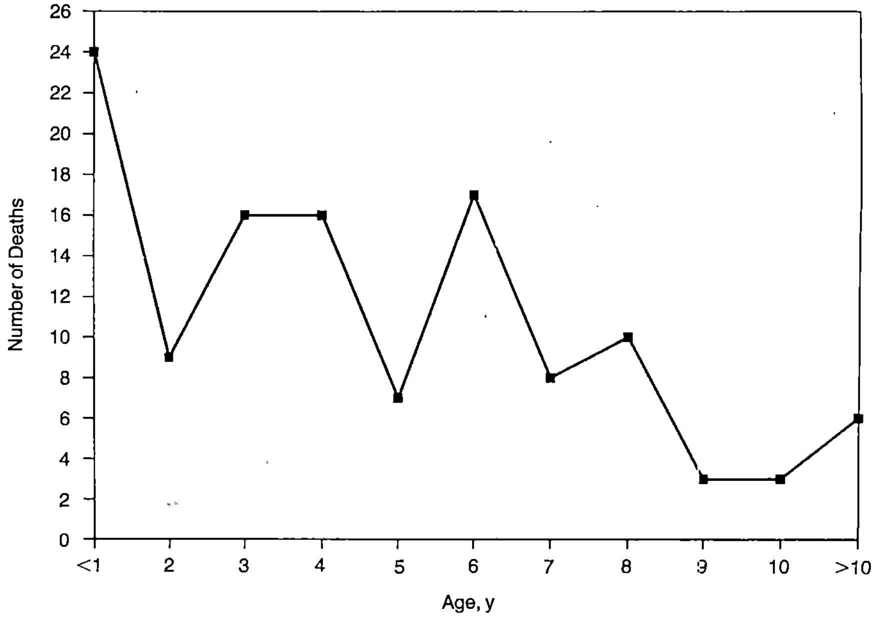

Fig 2.—Age distribution of 121 children who died by choking on rubber balloons or balloon pieces documented by the Consumer Product Safety Commission between 1973 and 1988.

COMMENT

Food objects such as hot dogs, candies, nuts, and grapes pose a far greater threat of death by choking to children than nonfood objects. However, of all children's products, balloons are the leading cause of childhood choking deaths in the United States. Although the number of cases reported is small, the incidence of these events is unquestionably more prevalent considering that the Canadian cases were traced by recall of the chief coroners and the CPSC database is not derived from statistical sampling.

The reasons why rubber balloons are particularly dangerous are not altogether clear. It may be that balloons are perceived, in general, as being safe toys for children, associated with festive occasions, and not as potential threats to life. They have a pleasant texture and appear to satisfy the oral exploratory needs of young children. Tragedies involving rubber balloons generally involve uninflated balloons or balloon pieces and tend to occur in one of two ways. Some children have died having sucked uninflated balloons into their mouths while trying to inflate them. Other deaths have occurred while children inhaled uninflated balloons that they were chewing, as did the first patient described above. The CPSC death file describes a young girl who was chewing an uninflated balloon when she fell from a swing. She hit the ground and reflexly inhaled and suffocated on the balloon. The last patient described herein illustrates that fatal accidents can occur even from inflated balloons.

The emergency management of acute upper airway obstruction due to a balloon aspiration is essentially similar to the treatment of any foreign body aspiration.[7] Because a medical history is often unavailable, as in the second patient reported, the diagnosis must be considered in all cases of sudden respiratory distress regardless of age. If the airway is not completely obstructed and there is good air exchange (forceful cough, wheezing inspiration, and loud cry) then the child should be allowed to continue with spontaneous efforts to clear the airway and should be immediately brought to an emergency department. If the balloon is visible, finger sweeps may be used to remove it. However, if it is not visible, blind finger sweeping may cause further impaction or reflex inhalation of the balloon into the trachea and should be discouraged.[8]

In the emergency department, conscious, coughing children with a suspected foreign body aspiration should be treated in the same way as children with acute epiglottitis. Preparations are made in anticipation of a possible complete obstruction. An anesthetist, otolaryngologist, pediatrician, and operating room nurses are summoned. Oxygen is administered continuously by mask if the child is cooperative, and the child is brought under anesthesia to the operating room for examination.

If there is poor air exchange (a weak or nonexistent cough) or total airway obstruction, then the Heimlich maneuver should be performed 6 to 10 times, followed by attempts at ventilation. In infants, abdominal thrusts may be traumatic, and back blows should be used instead. If there is no response to these procedures and the necessary equipment and personnel are available, direct visualization and removal of the balloon with a Magill's forceps or a rigid bronchoscope may be effective. Finally, an emergency tracheostomy is indicated if the above measures fail to establish a patent airway.

Spontaneous efforts and first-aid efforts, including the Heimlich maneuver, in dislodging balloons from the upper airway appear to be somewhat ineffective as illustrated in the patient reports above. This may be partly related to the collapsibility of latex balloons, allowing them to pass through the vocal cords and lodge at the carina. In addition, balloons, by their nature, are made to hold air inside and to prevent any air from passing through. Finally, well-meaning first-aid measures may actually prove to be more harmful than helpful. Two of the children described herein, who were initially partially obstructed but conscious, progressed to complete airway obstruction following blind sweeps of the pharynx. In another case, it was impossible to ventilate the lungs by a crycothyroidotomy. Tragically, it was later possible to remove the balloon from the trachea at autopsy by direct visualization and a Magill's forceps.

Without question, a complete ban on rubber balloons would have a major impact on choking deaths from children's products. Efforts designed to prevent traumatic events by influencing the behavior of caretakers and potential victims have not, in general, been successful.[9] Nevertheless, in the absence of a complete ban, the following guidelines may help reduce the risk of death from balloon aspiration:

1. Adults should always blow up balloons for children and supervise them while playing with them, taking special care to pick up and dispose of broken pieces of balloons. Older children should be warned of the dangers of chewing or sucking on ballons. A poster campaign warning parents and child-care attendants of the dangers of rubber balloons has been organized by the Edmonton Board of Health, Alberta.

2. We believe that rubber balloons should be banned from hospitals, day-care centers, and schools. In addition to preventing mishaps in public institutions (two of the four deaths in Canada occurred in the schoolyard), an institutional ban will alert parents and caretakers to the dangers of these objects.

3. In the United States, toy manufacturers and importers have been asked to put a safety warning message on balloon packages. This kind of approach, aimed at altering the behavior of caretakers and supervisors, has not been shown to be as effective as other passive preventive measures. This was recently demonstrated in the efforts to prevent deaths related to a toy missile-ejecting spacecraft.[10] Despite warning labels on the product, injuries and deaths continued to occur until the missile was withdrawn from sale due to consumer, media, and medical association pressure.

4. Redesigning common consumer products is also an effective preventive strategy. A CPSC review of objects that caused choking found that 70% were 19 mm or less in diameter, and 97% were 32 mm or less.[11] This resulted in the US Small Parts Regulation (effective January 1, 1981) whereby any toy or other children's article, or components or pieces of the article, fails to comply with this regulation if it fits entirely within a truncated cylinder with a 1.25-inch diameter and a depth ranging from 1.0 to 2.25 inches.[6] Balloons and balloon pieces cannot be tested in a meaningful way by the regulation as it is currently written. Innovative designs in balloons (eg, inclusion of a 33-mm ring or disk) could keep intact balloons from being aspirated but do not solve the problem of broken balloon pieces.[12] Helium-filled aluminum balloons are possible alternatives to rubber balloons on festive occasions. Death from suffocation has not been reported, to our knowledge, with this type of balloon, although the CPSC death file contains a report of a child who was strangled by the cord of a helium-filled balloon that was tied to her crib.

Finally, we should recognize that balloons pose a major hazard not only to our children but also to the environment. Birds, fish, and even a 590-kg leatherback turtle, found washed ashore in New Jersey, starved to death when balloons that were released into the atmosphere during celebrations lodged in their stomachs. An encouraging and positive development to protect both children and the environment is the action by the Governor's Highway Safety Program in North Carolina to stop using balloons as promotional exercises by state and local government agencies.[12]

We would like to thank Deborah Tinsworth, senior statistician, Consumer Product Safety Commission; Antoinette Rouget, MD; and Debbie Hayman for their help in the preparation of this manuscript.

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In Other AMA Journals

JAMA

Changing Patterns of Asthma Mortality
K. B. Weiss, D. K. Wagener (*JAMA.* 1990;264:1683)

Changing Patterns of Asthma Hospitalization Among Children: 1979 to 1987
P. J. Gergen, K. B. Weiss (*JAMA.* 1990;264:1688)

Attitudes of Internal Medicine Faculty and Residents Toward Professional Interaction With Pharmaceutical Sales Representatives
W. P. McKinney; D. L. Schiedermayer; N. Lurie; D. E. Simpson; J. L. Goodman; E. C. Rich (*JAMA.* 1990;264:1693)

Reflections on the Rise in Asthma Morbidity and Mortality
A. S. Buist, W. M. Vollmer (*JAMA.* 1990;264:1719)

The Status of Women at One Academic Medical Center
K. G. Nickerson; N. M. Bennett; D. Estes; S. Shea (*JAMA.* 1990;264:1813)

The Association of Cyclosporine With the 1-Year Costs of Cadaver-Donor Kidney Transplants
J. Showstack; P. Katz; W. Amend; O. Salvatierra (*JAMA.* 1990;264:1818)

An Interpretation of Michelangelo's Creation of Adam Based on Neuroanatomy
F. L. Meshberger (*JAMA.* 1990;264:1837)

Some People Are Dead When They're Cold and Dead
P. S. Auerback (*JAMA.* 1990;264:1856)

Disproportionate Septal Hypertrophy Associated With Erythroblastosis Fetalis

MAJ Brian S. Carter, MC, USA; Jane E. DiGiacomo, MD;
LCDR Scott M. Balderston, MC, USN; James W. Wiggins, MD; Gerald B. Merenstein, MD

• We retrospectively reviewed clinical and echocardiographic data on 10 newborns with erythroblastosis fetalis who were admitted to our nurseries between 1984 and 1988 and who required a double-volume exchange transfusion and neonatal intensive care. Echocardiograms were performed in the first 48 hours of life. In 5 patients, disproportionate septal hypertrophy was demonstrated; 1 additional patient had biventricular hypertrophy with a thickened septum but not disproportionate septal hypertrophy. The mean septal: left ventricular free-wall ratio for the group (n=10) was 1.37. No correlation was apparent between the occurrence of disproportionate septal hypertrophy and newborn glucose, bilirubin, or hematocrit values. When analyzed separately, the 4 patients who did not receive intrauterine blood transfusions had a ratio of 1.73±0.21 (mean±SEM); this was significantly greater than the ratio in the 6 patients who were transfused in utero (1.13±0.24). In patients who underwent transfusions, there was no correlation between the number of transfusions and the septal:left ventricular ratio. This study reports a significant but previously unrecognized cardiac hypertrophy with disproportionate septal hypertrophy in patients with erythroblastosis fetalis. Our data suggest a sparing effect of intrauterine fetal transfusions. The mechanism by which these transfusions may affect the hypertrophic development of the myocardium remains to be determined.

(*AJDC.* 1990;144:1225-1228)

Neonatal disproportionate septal hypertrophy (DSH) represents a poorly understood hypertrophic development of the interventricular septum. While observed in infants born to diabetic mothers (IDM) more than a decade ago,[1-3] the causal mechanism for this condition has yet to be defined. An association with neonatal hypoglycemia in IDM and nesidioblastosis[4] suggests a role for fetal hyperinsulinism.

A recent case of DSH with associated biventricular hypertrophy and neonatal hypoglycemia in a newborn with erythroblastosis fetalis (EBF) prompted a retrospective study of echocardiographic findings in other patients with EBF. Recognizing that patients with EBF share many characteristics of IDM,[5-7] we sought to determine if there was an increased incidence of DSH in these patients.

PATIENTS AND METHODS

Entrance criteria for patients in this study consisted of all newborns with a diagnosis of EBF (regardless of the causative blood-group antigen) who were delivered in three Denver, Colo, area hospitals from January 1984 through July 1988 and who had echocardiographic studies performed in the newborn period. The diagnosis of EBF was based on the following factors: (1) known blood-group sensitization, from maternal antibody screening; (2) evidence of hemolytic disease either in utero or at birth (fetal hydrops was not required); and (3) findings from amniotic fluid optical density studies and use of the Liley curves.[8]

Patients were excluded if they had any congenital anomalies, including structural heart disease. Infants born to diabetic mothers were excluded because of the known increase of DSH in this population.

After identifying patients in the study group, a chart review was conducted to determine the following parameters: gestational age; birth weight; Apgar scores; initial hematocrit, total bilirubin, blood glucose (as determined by a reagent strip that used fingertip venous blood [Dextrostix]), and total protein (by refractometry) values; chest roentgenogram results; findings on clinical examination; and the number of intrauterine transfusions. All blood values were determined on umbilical cord blood specimens or within the first 4 hours of life before a double-volume exchange transfusion.

Tapes of echocardiograms were obtained and reviewed by a single pediatric cardiologist (J.W.W.) who was unaware of the patients' primary diagnoses or conditions. Measurements performed with the use of the parasternal long-axis view included the following: interventricular septal thickness, in millimeters, measured at the level of the papillary muscles; right ventricular free-wall thickness; and left ventricular (LV) posterior free-wall thickness at end-diastole, measured between the attachment of the mitral valve and the papillary muscles. The diagnosis of biventricular hypertrophy was made when both the right ventricular and LV thickness were 4.0 mm or more; DSH was defined as an interventricular septal: LV (S:LV) free-wall ratio of greater than 1.3:1.0. The normal value for this ratio is less than 1.3:1.0.[9]

Regression analysis of the S:LV wall ratio was performed with patient glucose, hematocrit, bilirubin, and total protein values and intrauterine transfusion status. A correlation coefficient of .6 or greater was considered to be suggestive of a relationship between any individual parameter and the S:LV ratio. Further analysis of two distinct patient groups was then undertaken. Group 1 patients (those with an S:LV ratio of <1.3:1.0, in the normative range) were compared with group 2 patients (those with an S:LV ratio of ≥1.3:1.0, DSH) by using the unpaired Student *t* test. Repeated comparison was undertaken for those patients who had received in utero transfusions against those who did not.

RESULTS

Ten patients were studied. These were taken from a total population of 20 patients with EBF in Denver area hospitals during the 5-year study period. Our study was limited, then, by the number of patients with EBF requiring neonatal intensive care who received an echocardiogram (for follow-up of intrauterine evidence of congestive heart failure, pericardial or pleural effusions, or cardiopulmonary signs warranting

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From the Lubchenco Center for Perinatal Research (Drs Carter and Merenstein) and Department of Pediatrics (Drs DiGiacomo, Balderston, and Wiggins), University of Colorado School of Medicine, Denver.

The views of the authors do not purport to reflect the positions of the Departments of the US Army, US Navy, or Defense.

Reprint requests to Division of Perinatal Medicine, Box B-199, University of Colorado Health Sciences Center, 4200 E Ninth Ave, Denver, CO 80262 (Dr Carter).

Table 1.—Clinical Parameters of Patients Without DSH (Group 1) and With DSH (Group 2)*

	Group 1 (n=5)	Group 2 (n=5)
Antibodies	Rh anti–C and D (n=5), anti–Kidd (n=1)	Rh anti–C and D (n=3), anti–Kell (n=2)
Mean gestational age (range), wk	32.8 (29-37)	31.2 (25-34)
Mean ± SEM birth weight, g	2046 ± 270	2010 ± 217
Median Apgar scores		
1 min	2	2
5 min	6	6
Fetal hydrops	None	3 of 5
Ascites	4 of 5	5 of 5
Cardiomegaly on chest x-ray film	4 of 5	5 of 5

*DSH indicates disproportionate septal hypertrophy.

Table 2.—Laboratory and Echocardiographic Findings in Newborns With EBF*

	Transfused In Utero (n=6)	Not Transfused (n=4)	P†
Mean (range)			
Hematocrit	0.268 (0.10-0.45)	0.155 (0.06-0.28)	NS
Bilirubin, µmol/L	191.5 (70-653)	85.5 (15-135)	NS‡
Glucose, mmol/L	3.92 (2.52-7.28)	4.48 (1.12-7.28)	NS
Mean ± SEM			
Total protein, g/L	4.4 ± 0.5	4.1 ± 1.1	NS
S:LV ratio	1.13 ± 0.24	1.73 ± 0.21	<.005

*EBF indicates erythroblastosis fetalis; NS, not significant; S, septal; and LV, left ventricular.
†By Student's *t* test.
‡See text for explanation of elevated bilirubin levels in the group who underwent transfusions.

such) while they were in the neonatal intensive care unit. All echocardiograms were performed in the first 48 hours of life. No patients met the exclusion criteria of anomalies or maternal diabetes.

Table 1 gives descriptive data for patients in groups 1 and 2. Blood-group antibodies involved in these patients included anti–C and –D Rh antibodies in 8, 1 of whom also had anti–Kidd antibodies and anti–Kell antibodies in 2. Gestational ages were similar in the two groups, with a mean of 32 weeks in the entire population. Birth weights ranged from 1150 to 2820 g and were similar in the two groups. Apgar scores, reported as medians, were low in both groups: 1 minute, 2; 5 minutes, 6. There was no correlation of DSH with blood glucose, hematocrit, bilirubin, or total protein values. Ascites was a common clinical finding in both groups; fetal hydrops, however, was only seen in group 2. All but 1 of the 10 patients had cardiomegaly on a chest roentgenogram.

Table 2 compares patients who received an in utero transfusion, with those who did not. Data are reported as the mean with either the range or the SE noted. There were no significant differences between these two groups for hematocrit, bilirubin, glucose, or total protein values. Of note, one patient in the group with transfusions had a marked direct hyperbilirubinemia (level, 653 µmol/L); if this value is excluded, the mean for this group is 99 µmol/L. The difference in the S:LV free-wall ratio between these two groups was significant.

As depicted in Fig 1, an association of DSH, as defined by an S:LV ratio greater than 1.3:1.0, was apparent in those patients with EBF who were not transfused in utero. Those patients who did receive an in utero transfusion, with one exception, had a normal ratio. In five of these six patients, there was no significance to the actual number of transfusions.

A total of 5 patients had DSH, 1 of whom also had biventricular hypertrophy. One additional patient had biventricular hypertrophy with a thickened septum but not DSH. The mean S:LV ratio for the entire study population of 10 patients was 1.37:1.0, with a septal thickness of 4.8 ± 0.6 mm (mean ± SEM). In comparison, 10 age- and birth-weight–matched newborns from our nurseries (without EBF) had a mean ratio of 1.13:1.0 and a septal thickness of 3.3 ± 0.1 mm.

When analyzed separately, the 4 study patients who did not receive an in utero transfusion had a mean ratio of 1.73:1.0; this was significantly greater than the normal value of 1.13:1.0 in the 6 study patients who were transfused and the 10 unaffected newborns who were studied ($P<.005$, unpaired Student's *t* test). The mean septal thickness in the 4 study patients who were not transfused was 6.0 ± 0.4 mm (mean ± SEM); this was 1.5 times greater than that seen in the study patients who underwent transfusions and 1.8 that seen in the unaffected newborns. The LV posterior free-wall thickness was similar in all newborns who were studied (3.4 mm in patients with EBF who underwent transfusions, 3.5 mm in patients who did not undergo transfusions, and 3.6 mm in the unaffected newborns).

Follow-up studies were available in four patients. In three of these, the septal hypertrophy had resolved by 3 months of age.

COMMENT

The spectrum of cardiac involvement in EBF varies from none to congestive heart failure with pericardial effusions. Cardiomegaly, whether detected in utero or after birth, is generally viewed as a poor prognostic sign. However, no reports of echocardiographic assessments of cardiac structure or function exist in these patients. Our echocardiographic study of 10 patients with EBF demonstrates a significant but previously unrecognized hypertrophic development of the myocardium with DSH.

Naeye[6] reported an increased cardiac weight due to myocardial hypertrophy in a postmortem study of 23 infants with

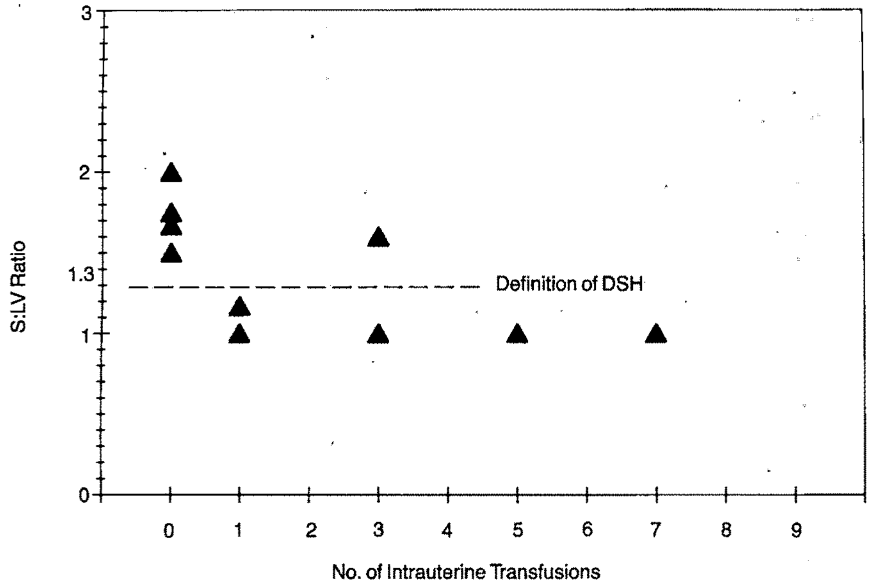

Fig 1.—Association of disproportionate septal hypertrophy (DSH) (septal:left ventricular [S:LV] ratio >1.3:1.0) with in utero transfusion status of 10 newborns (triangles) with erythroblastosis fetalis.

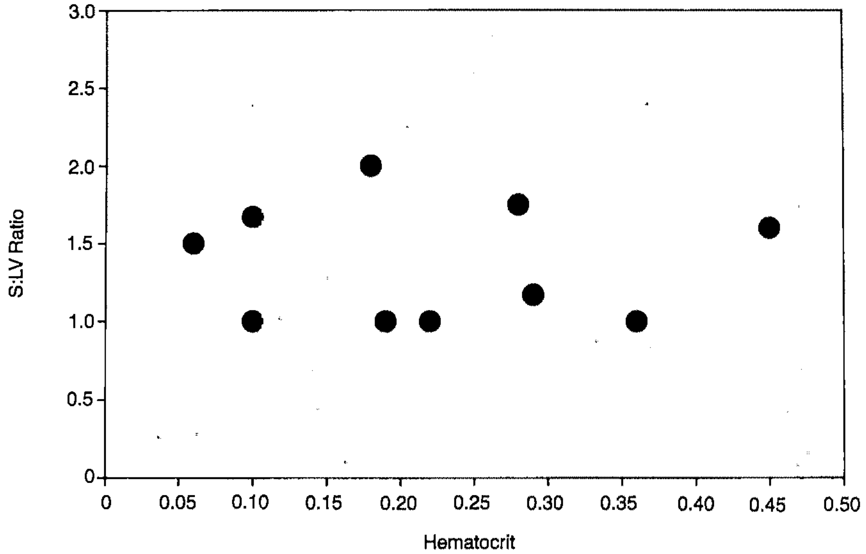

Fig 2.—Wide variation of newborn hematocrits seen in 10 newborns (circles) with erythroblastosis fetalis; no correlation with the septal:left ventricular (S:LV) ratio is apparent ($r = -.039$).

EBF. Increased cardiac work secondary to fetal anemia was speculated as the underlying mechanism. Should this be the case, infants with the most severe anemia would be expected to demonstrate the greatest degree of hypertrophy. Our data do not support this hypothesis as both biventricular hypertrophy and DSH were seen across a wide range of packed red blood cell volumes (6% to 45%) without any demonstrable correlation (Fig 2, $r = -.039$).

In our population, those patients who received an in utero transfusion had a significantly lower S:LV ratio. With one exception, they also had normal septal thickness. The fact that fetal transfusion has a sparing effect on hypertrophy of the myocardium, whereas the severity of anemia has no apparent relationship with this or the presence of DSH, suggests that other mechanisms are involved.

Erythroblastosis fetalis has been associated with both fetal[10] and neonatal hyperinsulinism and neonatal hypoglycemia.[6,11-13] Pancreatic islet cell hypertrophy has also been demonstrated in these patients.[5,7] These findings may be due to increased intravascular hemolysis with insulin inactivation,[14] placental insulinase activity,[11,15] or an unknown factor that may be produced in or transported across the placenta that stimulates excess insulin activity.[10] The elevation in fetal insulin levels may result in enhanced growth of the fetal myocardium. The role that in utero transfusion may play in affecting fetal insulin levels and diminishing hypertrophy of the septum is uncertain.

In the neonate, the myocardium is rich in insulin receptors.[16] In fetal life, it may be a particularly sensitive tissue to the trophic effects of hyperinsulinemia.[17] Based on works that demonstrated increased insulin receptor numbers and affinity in neonatal cells with a lack of "downregulation" despite an elevated insulin concentration,[18,19] Breitweser et al[4] proposed hyperinsulinemia to be an operative mechanism for the development of DSH in IDM. While the mechanism for the hyperinsulinism in EBF may be different from that seen in IDM, the possibility that it represents a common pathway for myocardial hypertrophy bears investigation.

Other models of DSH that may be associated with hyperinsulinism include infants born to mothers treated with β_2-sympathomimetic tocolytic agents and infants with nesidioblastosis. Such infants have demonstrated both cardiac septal hypertrophy[4,20] and hyperinsulinemia.[21,22] In our hospitals, we have performed echocardiographic studies in large-for-gestational-age infants born to nondiabetic mothers and found some to have DSH (R. R. Wolfe, MD, and J.W.W., unpublished data, January 1988 to July 1989). A recent study[23] suggests that these infants may also have elevated insulin levels.

In summary, cardiomegaly has been previously described in newborns with EBF and thought to be secondary to fetal anemia with subsequent high-output congestive heart failure. We have demonstrated echocardiographically that this cardiomegaly is associated with DSH and bears a resemblance to the well-described cardiomyopathy seen in IDM. A sparing effect is apparent in those patients with EBF who receive in utero transfusions. However, no correlation of septal thickness or the S:LV ratio with the neonatal packed red blood cell volume is present.

We hypothesize that fetal hyperinsulinism contributes to the development of septal hypertrophy and is likely to be a common cause for the observed DSH in infants with EBF and IDM. A prospective echocardiographic study of all infants with EBF (with and without an in utero transfusion), and other conditions with hyperinsulinism, is currently in progress to test this hypothesis.

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In Other AMA Journals

ARCHIVES OF SURGERY

Comprehensive Management of Renal Failure in Infants
David Tapper, MD; Sandra Watkins, MD; Mark Burns, MD; Robert O. Hickman, MD; Ellis Avner, MD (*Arch Surg.* 1990;125:1276-1281)

Extracorporeal Membrane Oxygenation in the Treatment of Neonatal Respiratory Failure
Robert P. Foglia, MD; H. Scott Bjerke, MD; Robert E. Kelly, Jr, MD; J. Duncan Phillips, MD; Eric W. Fonkalsrud, MD (*Arch Surg.* 1990;125:1286-1292)

Acquired Methemoglobinemia

The Relationship of Cause to Course of Illness

Jeffrey R. Avner, MD; Fred M. Henretig, MD; Constance M. McAneney, MD

• To better characterize methemoglobinemia in children, we reviewed the charts of 17 patients who were admitted to a children's hospital over the last 10 years. Two distinct groups were identified: (1) The *endogenous* group (n = 9) included patients with methemoglobinemia associated with an intercurrent illness. (2) The *exogenous* group (n = 8) included patients with methemoglobinemia secondary to drug exposure. Despite similar initial methemoglobin levels in the endogenous (mean, 29%) and exogenous (mean, 28%) groups, children in the endogenous group had more acidosis (serum bicarbonate levels of 5.9 vs 19.1 mmol/L and arterial pH of 7.01 vs 7.35). All the children in the exogenous group with methemoglobinemia secondary to an accidental ingestion stayed only 1 day in the hospital, while children in the endogenous group were admitted for an average of 19 days. Children with methemoglobinemia secondary to a drug exposure have a more benign illness with a shorter duration than children with methemoglobinemia associated with an intercurrent illness. It appears that the absolute level of methemoglobin is not as important as the underlying cause in determining both the course and severity of illness.

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Acquired methemoglobinemia occurs when an oxidant stress causes oxidation of heme iron to the ferric state, making it less able to bind with oxygen. This may occur after an acute overdose of an oxidant agent or in association with an intercurrent illness, usually gastroenteritis or metabolic acidosis. There are reports of methemoglobinemia secondary to drug exposure[1-5] or acidosis,[6] but no study has compared the two groups. We reviewed the charts of all patients with methemoglobinemia admitted over a 10-year period to a large, urban children's hospital to determine whether the presentation, severity of illness, and prognosis varied with the underlying cause.

PATIENTS AND METHODS

We reviewed the medical records of all children with methemoglobinemia admitted to the Children's Hospital of Philadelphia, Pa, from January 1979 through December 1988. Patients were selected after review of cooximetry records for methemoglobin levels greater than 3% in a peripheral blood sample. Two distinct groups were identified: (1) The *endogenous* group included patients with methemoglobinemia associated with gastroenteritis or dehydration. (2) The *exogenous* group included patients with methemoglobinemia secondary to drug exposure.

Data organization and analysis was done on the Epi Info System, developed by the Centers for Disease Control.[7] The Student *t* test was used to compare continuous data, and the two-tailed Fisher's Exact Test was used for categorical data.

RESULTS

Seventeen children with methemoglobinemia were identified. There were 10 boys (59%) and nine black children, and their mean age was 9 months (range, 5 days to 25 months). The clinical features and laboratory findings of all patients are summarized in the Table. Fourteen children were admitted through our emergency department, two children were transported from other hospitals directly to a patient care unit, and one child was an inpatient at the time methemoglobinemia developed.

Nine patients were classified in the endogenous group—seven presented with diarrhea and two presented with vomiting. Cyanosis was noted by the parent in only one case. Bacterial culture of the stool was negative in all cases. Seven children also had viral cultures of the stool, which were negative. Of the eight patients in the exogenous group, six cases were the result of accidental ingestion (phenazopyridine hydrochloride, five patients; benzocaine, one patient). Two cases were due to iatrogenic events: methylene blue injected in utero to a 32-week-old premature infant for evaluation of an amniotic fluid leak (patient 11), and topical benzocaine used for upper gastrointestinal tract endoscopy in a child with failure to thrive (patient 17).

Children in the endogenous group were younger (mean age, 3.3 vs 15.3 months), more often male (seven [78%] of nine vs three [39%] of eight children), and more often black (seven [78%] of nine vs two [25%] of eight children). Despite similar initial methemoglobin levels in the endogenous (mean, 29%; range, 10% to 66%) and exogenous (mean, 28%; range, 4% to 60%) groups, children in the endogenous group had more acidosis (serum bicarbonate level, 5.9 vs 19.1 mmol/L [$P<.0001$]; arterial pH, 7.01 vs 7.35 [$P<.001$]). The peripheral white blood cell count was higher in the endogenous group (30.6×10^9/L vs 11.5×10^9/L [$P<.001$]), as was the platelet count (813×10^9/L vs 369.5×10^9/L [$P<.001$]), but there was no difference in the hemoglobin concentration (112 vs 110 g/L).

Ten children received methylene blue intravenously—nine had methemoglobin levels over 25%, and one was symptomatic, with a methemoglobin level of 13%. Ten children underwent hemoglobin electrophoresis (cellulose acetate); none of these procedures showed altered structure of the hemoglobin mole-

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From the Division of General Pediatrics, the Children's Hospital of Philadelphia, and the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia. Dr Avner is now with the Division of Pediatric Ambulatory Care (Emergency Medicine), Department of Pediatrics, Albert Einstein College of Medicine/Bronx (NY) Municipal Hospital Center.

Reprint requests to Jacobi Hospital, Room 1W20, Pelham Parkway and Eastchester Road, Bronx, NY 10461 (Dr Avner).

Clinical Features and Laboratory Findings*

Patient No.	Cause	Age at Presentation, mo	Sex	Race	Methemoglobin, %	Arterial pH	Sodium Bicarbonate, mmol/L	White Blood Cells, $\times 10^9$/L	Hospital Stay, d	Intensive Care Unit Stay, d
1	Endogenous	1.5	M	B	.10	6.83	3	30.5	75	17
2	Endogenous	1.0	M	B	.10	7.11	4	39.3	10	3
3	Endogenous	0.5	M	B	.13	6.99	10	25.9	14	0
4	Endogenous	8.0	M	B	.15	7.18	6	24.0	26	0
5	Endogenous	2.0	F	B	.15	7.13	14	21.1	4	0
6	Endogenous	1.0	F	W	.33	6.95	2	41.8	12	4
7	Endogenous	1.0	M	W	.49	7.18	4	28.9	6	2
8	Endogenous	7.0	M	B	.54	6.95	2	40.2	13	13
9	Endogenous	8.0	M	B	.66	6.91	8	24.1	8	3
10	Exogenous	22.0	F	B	.40	ND	21	11.1	1	0
11	Exogenous	0.2	F	B	.21	7.35	18	7.7	30	13
12	Exogenous	25.0	F	W	.22	7.35	16	16.4	1	0
13	Exogenous	18.0	M	W	.26	7.40	21	14.8	1	0
14	Exogenous	8.0	F	W	.27	7.38	19	ND	1	0
15	Exogenous	25.0	F	W	.32	7.32	20	ND	1	0
16	Exogenous	16.0	M	W	.35	ND	16	9.9	1	1
17	Exogenous	8.5	M	W	.60	7.45	22	8.8	15	0

*ND indicates not determined.

cule (hemoglobin M). In three children in the endogenous group, the methemoglobin reductase level was also measured; results were normal for age. No child in either group had a relapse of the methemoglobinemia.

The average hospital stay for children in the endogenous group was 19 days. All six children in the exogenous group with methemoglobinemia secondary to accidental ingestion stayed 1 day in the hospital. Because of their underlying disease, children with methemoglobinemia secondary to therapeutic misadventures (patients 11 and 17) were admitted for a longer time, although the methemoglobinemia resolved within 1 day.

COMMENT

Primary methemoglobinemia involves congenital abnormalities in hemoglobin structure or inherited deficiencies of reduction enzymes; secondary methemoglobinemia is the result of a severe oxidant overload from acute poisonings or aberrations of metabolic state.[1] Transient methemoglobinemia with acidosis in infants has been described previously. In one study of 11 infants less than 3 months of age,[6] all had serum bicarbonate levels of less than 15 mmol/L (mean, 5.9 mmol/L) and elevated white blood cell counts (mean, 30×10^9/L). The cause of elevated methemoglobin in infants with acidosis and gastroenteritis has not yet been determined. It is thought that an unidentified oxidant is produced by the body in association with diarrhea, and the resulting acidosis may impair immature erythrocyte enzyme systems.[6] In contrast, an acute poisoning involves an exogenous oxidant stress to an otherwise healthy child. Various case reports have identified a variety of drugs involved in producing methemoglobinemia.[1-5]

In our study, children with methemoglobinemia secondary to acute poisoning had a shorter, more benign course of illness than children with methemoglobinemia associated with gastroenteritis and dehydration. This may reflect a relatively brief exposure to the oxidant stress in children with methemoglobinemia associated with acute poisoning, compared with ongoing exposure over a prolonged period in children with methemoglobinemia associated with gastroenteritis and dehydration. Also, children in the endogenous group tended to be much younger and perhaps were less able to compensate metabolically for the decreased oxygen-carrying capacity associated with methemoglobinemia. Thus, children in the endogenous group, who tend to be infants, may have both increased production and decreased destruction of methemoglobin,[6] while those in the exogenous group may have only increased production.

In light of these data, the methemoglobin level should be determined in a young infant with dehydration and severe acidosis who appears cyanotic or in whom acidosis persists despite adequate rehydration. Our experience suggests that the absolute level of methemoglobin is not as important as the underlying cause in determining both the course and severity of illness.

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Lead Poisoning and Thalassemia Trait or Iron Deficiency

The Value of the Red Blood Cell Distribution Width

Kanta Bhambhani, MB, BS, Regine Aronow, MD

• The cause of microcytosis and anemia in lead poisoning was investigated using red blood cell distribution width as a screening parameter in 21 consecutive patients with lead poisoning and seven nonrandomly selected patients with iron deficiency and lead poisoning. Of the 21 consecutive patients, 11 had microcytosis as defined by a mean corpuscular volume of less than 72 fL, nine had thalassemia trait (α or β), one had both α thalassemia trait and iron deficiency, and one had iron deficiency. The red blood cell distribution width was less than 17.0 in those with thalassemia trait and greater than 17.0 in the iron-deficient subjects. Results of our study suggest that microcytosis in children with lead poisoning is due to coexistent iron deficiency or thalassemia trait. The red blood cell distribution width may be of value in the rapid assessment of the cause of microcytosis in children with lead poisoning.

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Recent reports[1-3] suggest that microcytosis and anemia occur much less commonly in childhood lead poisoning uncomplicated by iron deficiency or thalassemia trait than previously reported. There is accumulation of erythrocyte protoporphyrins in both lead poisoning and iron deficiency owing to impaired heme synthesis. In the former, protoporphyrins accumulate because of inhibited ferrochelatase. In the latter, accumulation is caused by decreased availability of iron. Thus, free erythrocyte protoporphyrin (FEP), which is used to distinguish iron deficiency from thalassemia trait in patients with microcytic anemia, cannot be used for this purpose in patients with lead poisoning. The red blood cell (RBC) distribution width (RDW), readily measurable with automated electronic particle counters, is a quantitative measure of RBC size variation or anisocytosis. Red blood cell distribution width is elevated in iron deficiency (mean, 17.3), whereas it is normal or only mildly elevated in patients with thalassemia trait (mean, 15.2).[4-6] This study was undertaken to assess whether RDW could predict the cause of microcytosis in children with lead poisoning.

PATIENTS AND METHODS

Children referred to the Lead Clinic at Children's Hospital of Michigan, Detroit, during a 9-month period from March through December 1987 were evaluated prospectively. All children with blood lead levels greater than or equal to 1.20 μmol/L and FEP levels greater than or equal to 1.06 μmol/L were considered to have lead poisoning. Each patient had a complete blood cell count with RBC indexes and RDW determined by an electronic particle counter (Coulter S-Plus, Coulter Electronics, Inc, Hialeah, Fla).

Patients who had microcytosis, as defined by a mean corpuscular volume (MCV) of less than 72 fL,[7] were then evaluated for iron deficiency and thalassemia trait. Iron deficiency was indicated if serum ferritin levels were less than 10 μg/L and transferrin saturation was less than 15% or if the patient responded to iron therapy. Serum ferritin was measured by a two-site radioimmunoassay kit (Hybritech Tandem E Ferritin Antibody Kit, Hybritech, Inc, San Diego, Calif) based on the method of Miles et al.[8]

A diagnosis of β-thalassemia trait was made if hemoglobin (Hgb) A_2 levels were greater than 0.034 as measured by column chromatography. δ β-Thalassemia trait was diagnosed if fetal Hgb levels were greater than 0.020 as determined by alkali denaturation and normal Hgb A_2. Diagnosis of α-thalassemia trait (α-thalassemia-1) was made either by exclusion of β-thalassemia trait and iron deficiency or by the presence of trace amounts of tetrameric β-globin (Hgb H) inclusions on brilliant cresyl blue tests.[9,10] A low MCV-RBC ratio (Mentzer index, <13.5) was also used to distinguish iron deficiency from α- and β-thalassemia traits.[9]

Blood lead levels were measured by anodic stripping voltammetry as described by Morell and Giridhar.[11] Free erythrocyte protoporphyrin levels were measured by the acid extraction method as described by Piomelli et al.[12] All FEP units were expressed as micromoles per liter of packed RBCs.

RESULTS

Twenty-one consecutive children (20 black and one white) with lead poisoning who were referred to the Lead Clinic from March through December 1987 formed the study population. The children ranged in age from 15 months to 8.5 years. The blood lead, FEP, Hgb, MCV, and RDW values are shown in Tables 1 and 2. The cases were divided into two groups based on MCV levels. Group A (Table 1) included 10 children with normal MCV levels (>72 fL). Mean Hgb in this group was 122 g/L (range, 110 to 138 g/L). All had RDWs of less than 15.0 (range, 12.2 to 14.9). Group B (Table 2) included 11 children with MCV levels of less than 72 fL. Mean Hgb was 112 g/L (range, 83-128 g/L). The mean lead levels were 1.81 and 1.94 μmol/L in groups A and B, respectively. Table 2 also shows the RDW, serum ferritin, and quantitative Hgb A_2 and F determinations; MCV-RBC ratios (Mentzer index); and presence or absence of Hgb H inclusions in group B children. Seven

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From the Division of Hematology-Oncology (Dr Bhambhani), the Poison Control Center (Dr Aronow), and the Department of Pediatrics (Dr Aronow), Children's Hospital of Michigan, and the School of Medicine, Wayne State University, Detroit.

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Reprint requests to Children's Hospital of Michigan, 3901 Beaubien Blvd, Detroit, MI 48201 (Dr Bhambhani).

children (patients 11 through 16 and patient 20) were diagnosed as having α-thalassemia trait by the criteria defined above. Five of the seven also had Hgb H inclusions on brilliant cresyl blue tests. In addition, patient 20 had iron deficiency as evidenced by a high RDW and response to iron therapy. After 4 weeks of oral iron administration, Hgb levels in this patient rose to 110 to 120 μg/L, and RDW decreased to 15.0. MCV levels remained low, however, confirming the presence of thalassemia trait. Two additional children (patients 17 and 18) were considered to have either α- or β-thalassemia trait based on a Mentzer index of less than 13.5. Confirmatory tests were not obtained on their initial evaluations, and they were unavailable for follow-up. Patient 19 was diagnosed as having δ β-thalassemia trait as indicated by an elevated level of fetal hemoglobin (0.037) and a normal level of Hgb A_2 on hemoglobin electrophoresis. The RDW values in these children with thalassemia trait (patients 11 through 19) ranged from 13.6 to 16.6 (Table 2). Two children had iron deficiency (patients 20 and 21). Patient 20 had an RDW of 19.0 on the initial evaluation and was shown to have coexistent α-thalassemia trait and iron deficiency as described above. Patient 21 had iron deficiency, as indicated by a serum ferritin level of less than 3 μg/L, and had an RDW of 25.1.

Since the completion of this study of consecutive patients with lead poisoning, we have followed seven additional patients with documented iron deficiency and lead poisoning. The laboratory data are presented in Table 3. The mean RDW in this group was 18.6 (range, 17.7 to 20.1). The mean lead level was 2.52 μmol/L (range, 1.54 to 4.54 μmol/L). If the two patients with iron deficiency (patients 20 and 21, Table 2) are included with this group, the mean lead level is 2.51 μmol/L. This level is higher than the mean lead level of 1.81 μmol/L in the normocytic group (Table 1), but the difference is not statistically significant ($P = .06$, Student's t test).

Table 1.—Group A: Laboratory Data in Patients With Lead Poisoning and MCV >72 fL*

Patient No./ Age, mo	Lead, μmol/L	FEP, μmol/L	HGB, g/L	MCV, fL	RDW
1/58	2.22	6.35	125	77.9	14.5
2/103	2.07	1.59	131	83.9	12.2
3/40	1.20	1.13	138	75.6	12.8
4/59	2.27	5.22	122	86.4	14.4
5/33	2.02	0.83	120	79.4	13.1
6/39	1.30	2.38	110	74.4	14.2
7/37	1.73	2.54	118	77.4	14.9
8/46	2.22	5.46	123	80.0	13.5
9/62	1.35	1.77	116	78.9	14.4
10/15	1.73	0.60	119	80.4	13.3
Mean level	1.81	. . .	122	. . .	13.7

*MCV indicates mean corpuscular volume; FEP, free erythrocyte protoporphyrin; HGB, hemoglobin; and RDW, red blood cell distribution width.

COMMENT

In this study of children with lead poisoning, microcytosis was found to be due to either thalassemia trait or iron deficiency.

Nutritional studies reviewed by Mahaffey[18] have demonstrated that iron-deficient patients are likely to absorb larger portions of ingested doses of lead than non–iron-deficient patients. It then becomes critical to make the diagnosis of iron deficiency as soon as possible, because coexistent lead exposure and iron deficiency put children at a higher risk for lead poisoning . As discussed earlier, FEP levels cannot be used to make the diagnosis of iron deficiency in children with lead poisoning because FEP is elevated in both disorders. The RDW determination, however, has been used as a screening parameter in distinguishing iron deficiency

Table 2.—Group B: Laboratory Data in Patients With Lead Poisoning and MCV <72 fL*

Patient No./ Age, mo	Lead, μmol/L	FEP, μmol/L	HGB, g/L	MCV, fL	RDW	Mentzer Index, MCV/RBC	Ferritin, μg/L	HGB A_2/F	HGB H Inclusions	Diagnosis
11/45	2.36	4.17	127	70.9	15.7	12.7	43	0.020/<0.010	Positive	α-Thal trait
12/46	3.38	12.01	109	66.9	15.6	13.2	23	0.021/<0.010	Negative	α-Thal trait
13/46	2.22	8.63	93	65.5	14.6	13.3	31	0.022/<0.010	Positive	α-Thal trait
14/52	2.02	4.00	101	66.8	13.6	13.6	24	0.024/<0.010	Positive	α-Thal trait
15/19	1.54	4.33	110	60.6	16.6	10.7	18	0.026/<0.010	Positive	α-Thal trait
16/40	1.25	1.08	124	67.8	16.4	12.0	15	0.022/<0.010	Negative	α-Thal trait
17/21	1.35	5.06	117	67.1	16.0	12.2	ND	ND	ND	Probable thal trait
18/23	1.25	5.25	128	71.0	16.5	13.0	ND	ND	ND	Probable thal trait
19/34	1.88	1.52	118	70.7	13.8	13.9	14	0.025/0.037	Negative	δβ-Thal traits
20/34	1.49	3.64	98	60.7	19.0	11.8	ND	ND	Positive	α-Thal trait
20/41	1.11	4.58	86	56.7	20.5	. . .	17	ND	ND	Iron deficiency anemia
21/72	3.48	4.07	83	64.0	25.1	15.3	<3	0.022/<0.010	ND	Iron deficiency anemia
Mean level	1.94	. . .	112	. . .	16.9	. . .	. . .	. . .	. . .	. . .

*MCV indicates mean corpuscular volume; FEP, free erythrocyte protoporphyrin; HGB, hemoglobin; RDW, red blood cell distribution width; RBC, red blood cell count; Thal, thalassemia; and ND, not done.

Table 3.—Non-Consecutive Patients With Lead Poisoning and Iron Deficiency*

Patient No.	Lead, µmol/L	FEP, µmol/L	HGB, g/L	MCV, fL	RDW	Ferritin, µg/L	Transferrin Saturation, %
1	2.31	7.27	86	50.0	20.1	9	. . .
2	2.99	6.08	110	61.1	17.7	. . .	0.043
3	2.60	3.92	98	63.6	17.7	. . .	0.015
4	1.88	1.87	111	67.5	17.9	. . .	0.068
5	4.54	15.93	82	49.0	19.8	. . .	0.072
6	1.78	2.76	111	67.0	17.8	3	0.108
7	1.54	2.24	112	69.0	19.3	. . .	0.111
Mean level	2.52	. . .	101	. . .	18.6	. . .	. . .

*FEP indicates free erythrocyte protoporphyrin; HGB, hemoglobin; MCV, mean corpuscular volume; and RDW, red blood cell distribution width.

from other causes of microcytic anemia[5,6] and is available at no additional cost to the patient. In our study population, children with lead poisoning who had normal MCV levels had RDW values in the normal range (<15.0). The RDW in patients with thalassemia trait was less than 17.0, except for one patient who had coexistent iron deficiency. In this study, 7 (33%) of 21 black children had α-thalassemia trait, presumably of the two-gene deletion type (α-thalassemia-1), as judged by the presence of microcytosis and Hgb H inclusions. This high incidence of α-thalassemia-1 compared with the published frequency of 1% to 3% in blacks[14] was entirely unexpected, and further confirmation by α-globin gene analysis would be useful. The mean RDW of the nine patients with iron deficiency in this study was 19.3 (range, 17.7 to 25.1). The mean blood lead level of our iron-deficient patients was higher than, but not significantly different from, the blood lead levels in the non–iron-deficient patients. This may be due to the relatively small sample size. Alternatively, the routine screening procedures identify patients before the full effects of iron deficiency on lead absorption are evident.

Our study confirms and extends prior observations[1-3] that microcytosis in children with lead poisoning is not due to lead, but reflects concomitant iron deficiency or thalassemia trait (α or β). Among the patients with microcytosis, RDW separated patients with iron deficiency (RDW >17.0) from patients with thalassemia trait (RDW <17.0). In those patients with RDW values of more than 17.0, iron deficiency is highly likely, and a therapeutic trial of iron is justified. Also, an investigative workup for thalassemia trait is recommended in children with lead poisoning if microcytosis persists after iron treatment.

Laurie Hetchler, Virginia Cosgrove, and Julie Nucci helped prepare the manuscript. Martin J. Hogan, PhD, helped with the statistical analysis.

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Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia, Pa
Harold Levine, MPA, Galveston, Tex
Barbara Starfield, MD, Baltimore, Md
Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*We, as pediatricians, are well aware of the problems with alcohol. Yet, this study shows that we do not necessarily carry this into our practices. Our colleagues in family practice do. What is the difference? Does it take a personal experience with the problem to make us get involved? Read this and see if it applies to your practice.*—H.D.A.

Pediatricians' Knowledge and Practices Regarding Parental Use of Alcohol

Steven W. Greer, MD; Howard Bauchner, MD; Barry Zuckerman, MD

• Problems with alcohol are common in the United States but are too frequently ignored by physicians, particularly those working with children. We explored pediatricians' knowledge and practices regarding parental use of alcohol and compared these attributes with those of family practitioners. Child health care providers attending three continuing medical education courses in general pediatrics were surveyed using a closed-item questionnaire. One hundred ninety (69%) of the participants responded, including 90 pediatricians and 39 family practitioners. Forty-six percent of responding pediatricians, compared with 90% of family practitioners, stated that they ask about problems with alcohol in taking a routine family history. Thirty-eight percent of pediatricians who knew the frequency of alcoholism, compared with 47% of those who did not, indicated that they include it in taking a routine family history. Forty-six percent of pediatricians who have experienced a problem with alcohol in their own family, compared with 20% of pediatricians without such personal experience, routinely address the issue of alcohol use with parents and children. Similar analyses among the family practitioners revealed no significant differences. We conclude that fewer than half of pediatricians ask about problems with alcohol in taking a family history. The likelihood of asking about such problems was not influenced by the health care provider's knowledge of alcoholism, but it was influenced by the provider's personal family history of problems with alcohol. Because of the important morbidity associated with alcohol use in families, and because intervention can improve functioning and adaptation of the child, training and Continuing Medical Education courses should address this issue.

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Alcoholism is widespread in our society. One in eight adults in the United States is an alcoholic,[1,2] and one in six children has a parent who is alcoholic.[3] Children in alcoholic families are exposed to biomedical factors (eg, genetic and in utero exposure) and social factors (eg, parenting and family dysfunction) that place them at increased risk of developmental and behavioral problems.

A review of the literature reveals the wide range of important morbidity experienced by the children of alcoholic families. In utero exposure to meaningful amounts of alcohol with other associated risk factors, resulting in the fetal alcohol syndrome or effects, has devastating consequences.[4,5] Much more common are the effects of postnatal alcohol use on parenting behavior and the home environment.[6-8] Preschoolers are at increased risk of child or sexual abuse,[9] and school-age children exposed to problems with alcohol in their family manifest more psychosomatic illnesses[10]; emotional, anxiety, and conduct disorders[11,12]; and school problems,

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From the Divisions of General Pediatrics (Drs Greer and Bauchner) and Developmental and Behavioral Pediatrics (Drs Bauchner and Zuckerman), the Department of Pediatrics, Boston (Mass) City Hospital and the Boston University School of Medicine; and the School of Public Health, Boston University (Drs Bauchner and Zuckerman).

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Reprint requests to the Department of Pediatrics, Boston City Hospital, 818 Harrison Ave, Boston, MA 02118 (Dr Greer).

including hyperactivity,[13,14] compared with children whose parents do not have problems with alcohol. Adolescent children of alcoholic parents demonstrate more emotional problems and antisocial behavior, including alcohol and other drug use and school suspension.[11,15] When children of alcoholic parents reach adulthood, they may continue to or begin to manifest problems, including marital problems and an increased risk of alcohol or other drug abuse.[16,17]

Evidence shows that if these families and children are identified early, some of the morbidity can be avoided. For example, individual psychotherapy,[18] school-based group therapy,[19] self-help groups such as Alateen,[20] children's literature,[21] and family therapy[7] have all been shown to help children.

Parental problems with alcohol are common, cause important morbidity for children, and are amenable to intervention. We explored pediatricians' knowledge and practices regarding parental use of alcohol. We compared pediatricians to family practitioners (FPs) to highlight differences in knowledge and practice. We hypothesized that (1) fewer pediatricians than FPs routinely address the issue of parental use of alcohol and (2) physicians who have experienced problems with alcohol in their own family would be more likely to address the issue of parental use of alcohol than would those without such problems.

METHODS

All child health care providers attending three continuing medical education courses in general pediatrics (November 1988 through May 1989) were eligible. The courses were located in Massachusetts, Vermont, and South Carolina. Two of the courses were organized by the Boston (Mass) University School of Medicine and one by the University of Massachusetts Medical Center, Worcester.

A 14-item, closed-ended questionnaire was developed for this study. It included questions addressing demographic information, the provider's knowledge and practices regarding parental use of alcohol, and whether anyone in the *provider's* family had a problem with alcohol. The questionnaire was distributed to all course participants with the course evaluation form; participants were urged to complete the questionnaires and return them along with the evaluation form. Participation in this study was anonymous and voluntary.

Table 1.—Providers Surveyed

Course	Total No. of Participants	Respondents*			
		Pediatricians	FPs	Other	Total
A	130	37	5	44	**86**
B	55	17	19	9	**45**
C	89	36	15	8	**59**
Total	**274**	**90**	**39**	**61**	**190**

*FPs indicates family practitioners; other, nurse practitioners, nurses, and residents.

Pediatricians and FPs were compared with regard to their knowledge of (1) the epidemiology of alcoholism and (2) the impact of parents' alcohol problems on childrens' behavior as well as (3) their reported practices regarding the inclusion of questions about alcohol use by parents and children and (4) the reported rates of problems with alcohol in the provider's own family. The responses of pediatricians and FPs were then analyzed separately, controlling for demographic, knowledge, and personal family history variables. Statistical analyses were performed with χ^2 or Fisher's Exact Test when cell sizes required its use.

RESULTS

Of the 274 participants in the three continuing medical education courses, 190 (69%) completed the questionnaire. We do not have data on the providers who did not complete the questionnaire. In this article, we report only on the pediatricians ($n=90$) and FPs ($n=39$) because of small numbers in the other groups (Table 1).

Pediatricians from the three courses did not differ significantly according to years in practice, type of practice, or whether they reported that someone in their family had a problem with alcohol; thus, they were combined into one group for subsequent analyses. Most pediatricians had been in practice for 5 to 15 years, and the majority were in private practice (Table 2). Nearly one third of pediatricians reported that someone in their own family had a problem with alcohol.

The groups of FPs from the three courses likewise did not differ significantly in years in practice, type of practice, or whether they reported that someone in their family had a problem with alcohol, and were similarly combined. Family practitioners were evenly distributed between groups having been in practice less than 5 years and 5 to 15 years. Like the pediatricians, however, the majority were in private practice and one third reported a personal family history of problems with alcohol.

Nine percent of pediatricians, compared with 15% of FPs, knew the frequency and sex ratio of alcoholism (P was not significant) (Table 3). Eighty percent of pediatricians and 85% of FPs knew that children of alcoholic parents are at increased risk of behavior problems and that they often do not talk spontaneously about their parents' problems with alcohol (P was not significant).

Pediatricians and FPs differed in their clinical practice regarding problems with alcohol. Forty-six percent of pediatricians in contrast to 90% of FPs reported that they ask about alcoholism in their routine family history ($P<.001$). Pediatricians and FPs did not differ in how frequently they reported routinely asking children about their *parent's* drinking (8% vs 15%) or in asking children or adolescents about their *own* drinking (74% vs 79%).

Because a physician's clinical approach to alcoholism may be influenced by many variables, including knowledge, length of time in practice, type of practice, and the personal family history of problems with alcohol, we repeated the analyses to investigate the impact of these factors. Pediatricians who knew more about alcoholism were no more likely to report that they include questions about alcoholism in the routine family history than were those with less knowledge about alcoholism. Thirty-eight percent of pediatricians who knew the frequency of alcoholism, compared with 47% of those who did not, include questions related to alcohol in the family history (P was not significant). Similarly, 47% of pediatricians who knew that children generally do not

Table 2.—Characteristics of Pediatricians and Family Practitioners (FPs)

Variable	No. (%) Pediatricians (n=90)	FPs (n=39)
Years in practice		
<5	24 (27)	18 (46)
5-15	42 (47)	16 (41)
>15	24 (27)	5 (13)
Type of practice		
Private	49 (54)	25 (64)
Health maintenance organization	14 (16)	6 (15)
Academic	12 (13)	3 (8)
Personal family history		
Yes	26 (29)	13 (33)

spontaneously talk about their parents' alcohol problems, compared with 44% of those who did not know this, include questions about alcoholism in the family history (*P* was not significant).

The presence of a problem with alcohol in the pediatrician's family appears to influence practice approach: 46% of pediatricians with such a problem in their own family routinely include questions about alcohol in the family history *and* ask the child about their own drinking, while only 20% of pediatricians without that personal experience ask these questions ($P<.05$). Like the group of pediatricians as a whole, however, the practice approach toward alcoholism in this group of pediatricians was not influenced by their level of knowledge about alcoholism.

Family practitioners were similarly compared on these same measures of knowledge and practice approach to alcohol problems, according to their years in practice, type of practice, and presence or absence of alcohol problems in their own family. No significant differences were found.

COMMENT

Our survey shows that fewer than half of the pediatricians in our study sample ask about problems with alcohol when taking a family history. The likelihood of asking about problems with alcohol did not appear to be influenced by the pediatrician's knowledge of alcoholism but rather by whether the pediatrician has a personal family history of problems with alcohol. More FPs than pediatricians ask about problems with alcohol, suggesting that training and practice orientation are also important.

Table 3.—Pediatricians and Family Practitioners (FPs) Compared on Knowledge and Practice Regarding Problems With Alcohol

	Pediatricians, % (n=90)	FPs, % (n=39)
Knowledge		
Epidemiology: frequency, sex ratio known	9	15
Behavior: increased risk of behavior problems and reluctance of children to talk about parental alcoholism known	80	85
Practice		
Include alcoholism in family history	46	90*
Ask child about *parents'* drinking	8	15
Ask child/adolescent about *own* drinking	74	79

*$P<.001$.

The observation that a minority of pediatricians address the issue of alcohol is consistent with previous studies of physicians working with adults.[22,23] One study found that only 10% of patients meeting diagnostic criteria for substance abuse or mental disorder were recognized by primary care physicians.[22] This highlights a limitation of our study: we relied on self-report to ascertain the behavior of physicians and may have overestimated how often they actually inquire about problems with alcohol. However, given this limitation, this is the only study we know of that addresses the question of pediatrician recognition of parental problems with alcohol.

To address effectively the issue of parental problems with alcohol, pediatricians need to be trained in the identification and management of the child exposed to parental alcoholism or abuse. However, the results of our study indicate that greater knowledge about alcoholism alone did not increase the likelihood of addressing this issue in the routine family history. This is consistent with a study by Warburg and colleagues,[24] who found that knowledge of alcoholism was not significantly related to medical residents' estimates of the prevalence of alcoholism among their patients, to their rate of treating alcoholic patients, or to their rate of referring patients for therapy for alcoholism.

In our study, pediatricians with a personal family history of problems with alcohol were more likely than others to address this issue clinically. Similarly, in the Warburg et al[24] study, supervised clinical experience with alcoholism was associated with higher rates of treating or referring patients for therapy for alcoholism. Thus, under certain conditions, including personal experience in a family with a problem with alcohol or having more supervised clinical exposure, it is possible to increase the likelihood of physicians to address this issue.

Two programs that involve the participants in active clinical training were established by Warburg et al[24,25] and Adger et al.[26] Warburg and colleagues trained their staff internists during weekly seminars for 6 months, a brief exposure to several approaches to treatment of alcoholism, and ongoing supervision of the participants' alcoholic patients. They also implemented a program for the medical residents in their five affiliated hospitals, including six 1-hour lectures and discussion sessions, followed by ongoing consultation, role playing, and case-related teaching about alcoholism in the residents' outpatient practice settings.[25] Subjective evaluation of these programs suggested improved diagnostic and management skills among participants.

Adger and colleagues[26,27] designed a program specifically for resident and practicing pediatricians to increase their knowledge and awareness of substance abuse problems among parents and adolescents, to enhance the participants' skills in interviewing and assessing their patients, and to familiarize them with available resources. While there is no direct hands-on clinical experience in this curriculum for the practicing pediatricians, the experience is made more dramatic and motivating through the use of videotapes and role-playing exercises. Evaluation of the impact of this curriculum is currently in progress.

Our study and others demonstrate that personal and clinical experience, rather than knowledge or attitudes, are the important variables in determining practice behavior regarding the use of alcohol. Clinical practice cannot be dependent on personal experience, however. Based on the model of the programs discussed above, we propose active training of pediatric interns and residents by concentrating on case-oriented history taking and management skills, in both the inpatient and outpatient settings. This training may involve such techniques as role playing and videotaping and would ideally be part of an integrated approach to behavioral and family issues.

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Articles

Home Care for Ventilator-Dependent Children

Psychosocial Impact on the Family

Richard D. Quint, MD, MPH; Elizabeth Chesterman; Lucy S. Crain, MD, MPH;
Marilyn Winkleby, PhD; W. Thomas Boyce, MD

• The impact of providing home care for ventilator-dependent children was studied in a cross-sectional survey of 18 northern California families. Through the use of a confidential structured interview and the Impact on Family Scale, we obtained information on family demographics; the childrens' medical conditions; financial, social, and personal impact on the family; and parental coping-mastery of the care of a ventilator-dependent child at home. Analysis of scores from the Impact on Family Scale showed no differences in the perceived family impact between primary caretakers and their spouses. Primary caretakers in the sample, however, showed significantly reduced Coping subscale scores with a longer duration of home ventilatory care. This finding, if confirmed in future studies, has policy implications for physicians and other health professionals working with ventilator-dependent children and their families, especially those who care for children over long periods.

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The acuity of health care needs and the spectrum of care provided in the homes of children with chronic illness, disability, or both have changed dramatically in the past 20 years. Initiated by the technology and support services of the 1970s, services developed that enabled children with end-stage renal disease to be given extended home dialysis treatment.[1] The 1980s saw an increasing number of children who were dependent on a variety of technologic devices to support and maintain their lives. Home care for children is no longer restricted to the treatment of minor illnesses but now includes more complex services such as apnea monitoring, intravenous therapy, tracheostomy and gastrostomy care, as well as more sophisticated technologic support for children who are chronically ill and dependent on the benefits of technologic innovations.

Increasing interest in home care for technology-dependent children arose from a combination of rising hospital costs, reduced payments by private and public payers, increased numbers of survivors of serious pediatric illnesses, and adverse effects of prolonged hospital stays on normal child development. Support for pediatric home care was fueled by the US Surgeon General's Conference in 1982[2] and has since been advocated by parents, insurers, hospital administrators, and medical personnel. In the United States, there is a small, but growing, population of children discharged from hospitals receiving assisted ventilatory therapy,[3] with their care at home reported as resulting in lowered costs[4] and improvement in their medical condition and developmental outcomes.[5] Little research has been done comparing the efficacy of home- vs hospital-based care of technology-dependent children[2] or the impact of home ventilatory care on their families.

Organized home care programs for these children and their families began in the late 1970s and today are available only in certain states.[6] California, the site of this study, has no statewide program designed to serve families with children who are ventilator dependent. Because increasing numbers of these children will be cared for by physicians in all states, it has become important to identify these families and to understand the family impact of caring for a ventilator-assisted child in the home. This study describes the status and impact of home care for ventilator-dependent children on families in northern California.

PATIENTS AND METHODS

This investigation was completed with the approval of the Committee on Human Research of the University of California, San Francisco, Medical Center. The target population consisted of infants and children from northern California, aged 9 months to 18 years, discharged to home care from neonatal or pediatric intensive care units or pediatric wards from 1975 to 1983. All were ventilator dependent, ie, required assisted ventilation for some or all of each day. The sample was identified by one of us (R.D.Q.) through contact with pediatric tertiary care facilities, individuals from the Northern California Network of Pediatric Intensive Care Units, and the California Children's Services Program. Nineteen families with a total of 20 ventilator-dependent children were identified and asked to participate in the study by written communication and follow-up telephone calls. One family whose child died before completion of the study, but was alive when the family agreed to participate, was included. Another participating family, similar to those in the sample, had a set of ventilator-dependent twins who, for study purposes, we describe as 1 child. Only 1 family declined to participate, leaving 18 families as the sample population. Written consent for participation was obtained from one or both parents.

In May and June 1987, the parent identified as the ventilator-dependent child's primary caretaker and, when possible, his or

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From the Divisions of General Pediatrics (Drs Quint and Crain) and Behavioral and Developmental Pediatrics (Ms Chesterman and Drs Winkleby and Boyce), University of California Medical Center, San Francisco.

Reprint requests to Department of Pediatrics, Mount Zion Hospital of the University of California—San Francisco, PO Box 7921, San Francisco, CA 94120 (Dr Quint).

her spouse were surveyed using a structured interview and a self-administered questionnaire. Interviews were completed in the homes of 15 families and by telephone in 3 families because of their distance from the San Francisco Bay Area. We employed a modified version of a structured interview designed by the Children's Home Health Network of Illinois for families with children receiving home ventilatory therapy (Kathleen E. Murphy, PhD, written communication, March 6, 1987). This yielded demographic and health data about the child and his or her family as well as specific information about home ventilatory care, duration of treatment, nursing care, insurance coverage, and unreimbursed costs of care.

In addition, a self-administered questionnaire, the Impact on Family Scale,[7] provided information on the personal and economic impact of a child's chronic illness by measuring a parent's perceptions of the impact on the family. The scale consists of 23 items assessing general impact or strain on the family, disruption of social relations, financial impact, and coping-mastery abilities. Minor adaptations of several items were made to reflect the child's condition of requiring ventilatory assistance rather than having a chronic illness. Items are scored on a Likert scale. The total and subscale scores are an arithmetic sum of respective items, with a higher score indicating greater negative impact. The Coping subscale, however, is reverse coded, and a higher score indicates better coping or mastery of the stress of illness.

RESULTS

This study employs only descriptive statistics, including simple *t* tests of differences between groups. In one instance, described below, χ^2 analysis was necessary. Interpretation of all results is based on the caution that these are exploratory analyses drawn from a small sample.

Demographics

The demographics of the northern California families with ventilator-dependent children are given in Table 1. Fifty-five percent (10/18) of the children were younger than age 6 years (mean age, 7 years). There were almost twice as many boys as girls in the study population. All but one of the families was intact with at least two adults in the household. Only one of the parents was divorced, and two other mothers had remarried when interviewed. The mean length of education of the primary caretaker was 12.7 years, with similar educational levels having been attained by the spouses (data not shown).

The medical profile of the children in the study is given in Table 2. Central nervous system conditions (central hypoventilation, neuromuscular disease, or Chiari malformations) were the predominant diagnoses in these children, accounting for 67% (12/18) of the primary conditions affecting them. Almost 30% (5/18) became ventilator dependent as a sequela of high cervical spine injury, and only one child had chronic lung disease. Eighty-three percent (15/18) of the children had one or more concomitant medical conditions, such as seizures, feeding problems, spasticity, or developmental delays. The mean age at which these children required assisted ventilation was 3.1 years.

Each family experienced some kind of difficulty with their equipment or suppliers (vendors). In the year before the interview, equipment problems such as power failures, improper mechanical function, monitor malfunctions, or difficulties with vendors occurred up to 20 times for two thirds of the families.

Table 3 describes financial and nursing issues. Fifty percent of the families relied on Medicaid funds (Medi-Cal) to cover the costs of home care, while 44% had either private insurance or were covered through a health maintenance organization. Only one family relied exclusively on Title V (California Children's Services Program) funds. Forty percent of the families had between 60% and 80% of their child's medical costs covered by insurance, and 60% had between 80% and 100% covered. Every family described extra out-of-pocket expenses in relation to their child's home care, with 83% spending $1000 or more for expenses resulting from essential home care needs in the 12 months before being interviewed.

In-home nursing care was an important issue for many of these families: at the time of interview, 72% had in-home nursing for 9 or more hours daily, and only 17% had no in-home nursing (Table 3). Seventy-one percent of the parents felt that having had nurses come to their homes to assist in the care of their children had invaded their privacy. However, in response to a specific follow-up question in the structured interview, the 15 families that currently had home

Table 1.—Characteristics of Children Receiving Home Ventilatory Care and Their Families

	No. (%)
Age, y	
<1	1 (5.6)
1-2	4 (22)
3-5	5 (28)
6-10	4 (22)
11-20	4 (22)
Sex	
M	11 (61)
F	7 (39)
Race	
B	6 (33)
W/non-Hispanic	10 (56)
Other	2 (11)
No. of adults in household	
1	1 (5.6)
2	13 (72)
≥3	4 (22)
Gross income	
<$20 000	7 (39)
$20 000-$30 000	5 (28)
>$30 000	6 (33)
Marital status of parents	
Married	17 (94)
Divorced	1 (5.6)
Education of primary caretaker, y	
<12	3 (17)
12	4 (22)
>12	11 (61)

Table 2.—Medical Profiles of Children Receiving Home Ventilatory Care

	No. (%)
Original medical condition	
Central hypoventilation	8 (44)
Trauma	5 (28)
Neuromuscular disease	2 (11)
Arnold-Chiari malformation	2 (11)
Bronchopulmonary dysplasia	1 (5.6)
No. of other medical conditions present at time of interview	
0	3 (17)
1-4	9 (50)
>4	6 (33)
Age when first required assisted ventilations	
<1 mo	6 (33)
1-12 mo	4 (22)
1-4 y	3 (17)
>4 y	5 (28)
Duration of home ventilation, y	
<1	5 (28)
1-4	8 (44)
≥5	5 (28)
Daily assisted ventilation, h	
<8	2 (11)
8-12	9 (50)
13-23	2 (11)
24	5 (28)
Equipment problems (year prior to interview), times	
1-5	3 (17)
6-10	6 (33)
11-20	3 (17)
>20	6 (33)
Type of health provider	
None	1 (56)
Pediatrician	4 (22)
Family practitioner	1 (56)
Pediatric subspecialist	12 (67)

Table 3.—Financial and Nursing Supports of Children Receiving Home Ventilatory Care*

	No. (%)
Financial	
Insurance coverage	
Private	4 (22)
HMO	4 (22)
Medicaid (Medi-Cal)	9 (50)
CCS	1 (5.6)
% of medical costs covered by insurance	
60-80	7 (39)
80-100	11 (61)
Nonreimbursed expenses (12 mo before interview)	
\$0-\$999	3 (17)
\$1000-\$1999	9 (50)
≥\$2000	6 (33)
Nursing	
Average h/d of home nursing	
0	3 (17)
1-8	2 (11)
9-16	9 (50)
17-24	4 (22)
Lack of privacy (n = 17 families)	
With spouse	
Yes	12 (71)
No	5 (29)
With children	
Yes	7 (41)
No	10 (59)
With friends	
Yes	4 (24)
No	13 (76)

*HMO indicates health maintenance organization; CCS, California Children's Services Program.

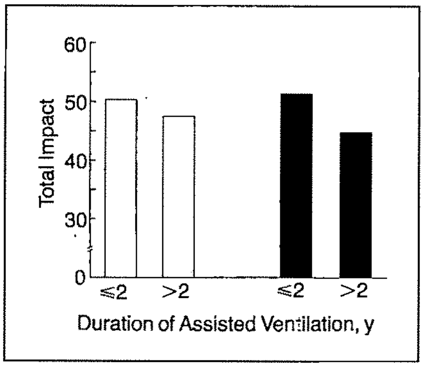

Fig 1.—Total impact vs duration of home ventilatory care for primary caretaker (open bars) and spouse (closed bars); higher score indicates greater negative impact. Neither difference was significant.

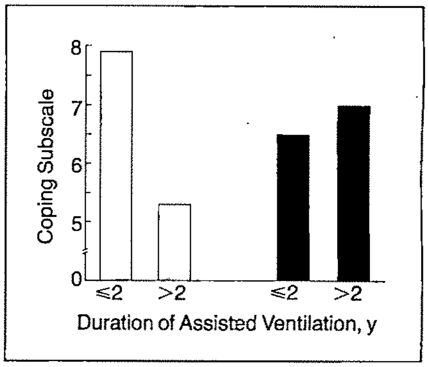

Fig 2.—Coping subscale scores vs duration of home ventilatory care for primary caretaker (open bars; $P<.001$) and spouse (closed bars; not significant); higher score indicates better coping-mastery.

nursing care emphasized their reliance on it (data not shown). Forty-four percent (n = 8) of the primary caretakers reported having no other family member or friend to assist in the nursing care of their children, and 40% had only their spouses available to help with this care (data not shown).

Impact on the Family

Severity of impact on the primary caretaker and the spouse as measured by the Impact on Family Scale were the same ($t=0.51$, $P=.62$, not shown). When the sample was stratified for level of education, there was a trend toward greater total impact ($t=1.96$, $P\leq.07$), greater personal strain ($t=1.86$, $P\leq.08$), and greater disruption of social relations ($t=1.94$, $P\leq.07$) for those primary caretakers with more than 12 years of education (data not shown). Such trends should be examined further in more formal studies with larger sample sizes.

Stratification of the sample by the length of time the child required in-home assisted ventilation revealed that the total impact did not change for either the spouse or the primary caretaker (Fig 1). However, the primary caretaker's Coping subscale score was significantly less when the duration of in-home ventilation was greater than 2 years (Fig 2). With increased duration of assisted ventilation for the child, there was no significant change in the Coping-Mastery subscale score for the spouse. For the primary caretaker, however, this subscale score was significantly poorer when the child had received home ventilatory care for longer than 2 years ($t=4.2$, $P<.001$).

The Coping-Mastery subscale of the Impact on Family Scale contains items that focus on strategies family members use to cope with the stresses of a child's illness: spouse and family support, promotion of normalcy of the child, and increased self-esteem gained by managing the child's condition.[7] Insight into the sources of the reduced Coping subscale scores described above in families with children receiving home ventilatory care for longer than 2 years was gained by examining each item on the subscale. Primary caretakers whose children required in-home ventilatory care for greater than 2 years had significantly poorer scores on items that measured family closeness ($t=2.4$, $P=.03$) and self-esteem resulting from caring for a child at home ($\chi^2=7.3$, $P<.03$). It was necessary to employ the χ^2 test of the difference between the two ventilation duration groups on the self-esteem variable because its structure did not permit use of the t test.

COMMENT

This descriptive epidemiologic study of northern California families with children who are ventilator dependent resulted in a particularly interesting finding. Examination of individual Coping subscale scores from the Impact on Family Scale showed no difference in spouse scores between families with a short vs long duration of in-home assisted ventilation. However, comparison of the primary caretakers' scores showed significantly lower Coping subscale scores among families whose children had required home ventilatory care for long durations. This latter finding is noteworthy because it was detected despite the small sample size and the low power of the study.

Why is the primary caretaker's coping reduced when the duration of the child's assisted ventilation is greater than 2 years? The combination of the amount of time spent in the sustained caretaker role and a long-term outlook of continued ventilator dependency may contribute to burnout and exhaustion. It also is possible that the longer durations of assisted ventilation result in greater uncertainty about the child's future. Others have commented on the psychological impact of uncertainty about a child's chronic condition,[8] and this may further contribute to reduced coping by the primary caretaker. The joint finding that (1) the impact on the family is maintained at a steady state over time and (2) this stability of family impact may be "purchased" at the expense of the primary caretaker's coping is a troubling result that needs further examination in a larger sample.

The results of this study may be of practical relevance to physicians who care for ventilator-dependent children. The findings may also be pertinent to those involved in the formulation of health policy for more broadly defined technology-dependent children. Recent work described agreement between mothers and physicians about the impact of a chronic illness on the child,[9] but physicians and mothers differed in their perceptions of the impact on other family members. An awareness of this difference and of the potential parental differences in coping with the situation of caring for a ventilator-dependent child would be important to take into account in caring for the child and working with the family.

If future work confirms a decline in coping among primary caretakers with long-term care, the use of ventilator technology in the home at the current level of intensity and complexity may need to be reevaluated. It may be important, for example, for the choices of care for technology-dependent children to extend beyond hospital or home-based care. Alternative settings, such as community-based extended care centers,[10,11] do not exist in northern California and may need to be an additional care option available at the time of discharge planning. Investigations of larger populations of ventilator-dependent children and longitudinal studies of their families are necessary to delineate these issues more clearly and to assess more completely family needs and parental differences in the ability to cope with the long-term care of ventilator-dependent children.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Strategies to Improve Teaching in the Ambulatory Medicine Setting
Linda G. Lesky, MD, Steven C. Borkan, MD (*Arch Intern Med.* 1990;150:2133-2137)

Vision Screening in a Primary Care Setting
Ellen Strahlman, MD, MHS; Daniel Ford, MD, MPH; Paul Whelton, MD, MSc; Alfred Sommer, MD, MSH (*Arch Intern Med.* 1990;150:2159-2164)

Neurodevelopmental Performance of Very-Low-Birth-Weight Infants With Mild Periventricular, Intraventricular Hemorrhage

Outcome at 5 to 6 Years of Age

Jean Lowe, PhD, LuAnn Papile, MD

• The neurodevelopmental outcome of 38 very-low-birth-weight neonates (birth weight, <1501 g) was followed up prospectively from birth to 5 to 6 years of age to assess the neurodevelopmental sequelae of mild periventricular, intraventricular hemorrhage (grades I and II). All neonates were screened for periventricular, intraventricular hemorrhage at 5 to 10 days of age. Eleven incurred a mild periventricular, intraventricular hemorrhage (group 1) and 27 had no periventricular, intraventricular hemorrhage (group 2). Each of the infants was neurodevelopmentally normal at 1 to 2 years of age. The 38 children were matched by race, age, sex, and socioeconomic status with control children (group 3) who had been born at term. On outcome measurements at 5 to 6 years of age, groups 1 and 2 scored significantly lower than group 3 on the combined test measurements and on three of the four individual measurements. Group 1 scored significantly lower than group 2 on the combined test measurements only. These data indicate that very-low-birth-weight infants are at risk for learning problems. Although children with mild periventricular, intraventricular hemorrhage did not demonstrate a significant deficit on individual test scores, the significant difference on the combined battery suggests that mild periventricular, intraventricular hemorrhage has an adverse effect on global performance.

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Over the past two decades, the impact of highly specialized obstetric and neonatal care has led to a dramatic reduction in neonatal mortality, especially for very-low-birth-weight (VLBW) infants (birth weight, <1501 g). As survival rates have increased, morbidity, particularly the neurodevelopmental sequelae of VLBW infants, has become an important issue.

The recent development and subsequent clinical application of noninvasive cranial imaging techniques have led to the recognition that periventricular, intraventricular hemorrhage (PIVH) occurs frequently in VLBW infants. Approximately 30% of all VLBW infants who are discharged to their homes from a tertiary care newborn intensive care unit have incurred PIVH.[1,2] Short-term follow-up studies of VLBW survivors with PIVH indicate that infants with moderate to severe PIVH have a higher prevalence of neuromotor and developmental handicaps at 1 and 2 years of age than do infants with mild PIVH or no hemorrhage.[3-8] In contrast, the outcome of VLBW infants with mild PIVH is similar to that of comparable infants with no hemorrhage.[3,4,8]

The long-term developmental outcome of VLBW infants who have incurred a PIVH is less well defined.[9-12] The purpose of the present study was to evaluate the neuropsychological outcome at 5 to 6 years of age in a group of children with and without mild PIVH who were developmentally normal at 1 and 2 years of age to determine if children with mild PIVH are at greater risk for learning problems than children without PIVH.

SUBJECTS AND METHODS

Population

The study group consisted of 38 children who had had birth weights less than 1501 g who had been admitted to the Newborn Intensive Care Unit at the University of New Mexico Hospital, Albuquerque, between 1977 and 1979. All of the neonates were appropriate for gestational age. Each was screened for PIVH with a computed tomographic brain scan at 5 to 10 days of age. If a PIVH was detected on the initial scan, weekly scans were done until the hemorrhage resolved. Based on the computed tomographic findings, the study group was subdivided into two groups: group 1 included 11 neonates who had a grade I PIVH (isolated subependymal hemorrhage) or grade II PIVH (intraventricular hemorrhage with no ventricular dilatation). Group 2 was composed of 27 neonates who did not incur a PIVH. Neither cerebral atrophy nor periventricular leukomalacia was evident in the neonates on computed tomography. The mean birth weight and gestational age, respectively, were 1137 g (range, 851 to 1361 g) and 30.5 weeks (28 to 34 weeks) for group 1 and 1157 g (624 to 1490 g) and 30.4 weeks (27 to 34 weeks) for group 2. All of the children had undergone a neurodevelopmental evaluation at 1 and 2 years of corrected age and were considered neurodevelopmentally normal. These children are a subset of the 198 VLBW infants whom we have followed up longitudinally since birth.[3] At the time of the test evaluation, none of the children had medical problems attributable to prematurity.

The control group (group 3) consisted of 22 children who were selected from a preschool or one of three elementary schools in the

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From the Division of Neonatology, Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque.

Reprint requests to Department of Pediatrics, University of New Mexico Hospital, 4 North, Albuquerque, NM 87131 (Dr Papile).

Albuquerque area. These children were matched with the study group by race, age, sex, and socioeconomic status as determined by the Hollingshead Scale.[13] All of the children in this group had been term, appropriate-for-gestational-age neonates who had had an uncomplicated perinatal and neonatal course. The study was approved by the Institutional Human Research Committee at the University of New Mexico School of Medicine, and informed parental consent was obtained for each child.

Method of Assessment

The assessment battery administered to each child included the following: the McCarthy Scales of Children's Ability,[14] a test of cognitive performance; the Test of Early Reading Ability,[15] a measurement of early reading skills; the Beery Developmental Test of Visual-Motor Integration,[16] a form-copying test designed to assess visuomotor integration; and Benton Finger Localization,[17] a tactile perceptual test designed to assess reading potential. One SD was used as the lower limit of normal performance on standard test scores. This corresponds to a general cognitive index (GCI) score of 85 on the McCarthy Scales of Children's Abilities, 85 on the Test of Early Reading Ability, and 7 on the Beery Developmental Test of Visual-Motor Integration.

Each child was individually tested for 60 to 90 minutes by a certified diagnostician (J.L.). To determine the reliability of the scoring, a second examiner independently scored 25% of the tests. Spearman Rank-Order correlation coefficients were obtained to estimate interrater reliability. All correlations obtained were greater than $r=.90$.

Method of Analysis

All values of the variables and their significant multivariate combinations were within +3 SDs of the mean for each group.[18] Cochran's Test indicated that the variances for each of the four measures were homogeneous.[19]

Multivariate analysis of variance[18] with planned contrasts was performed. The planned contrasts first compared the control group (group 3) with the children who were VLBW infants (groups 1 and 2). The children who were VLBW infants were then compared with each other (group 1 vs group 2). The four test scores were used as the dependent variables. Appropriate univariate analyses were completed with the Bonferroni adjustment for each of the analyses. Data analysis was performed utilizing SPSS statistical software (SPSS-X Inc, Chicago, Ill).

RESULTS

Children With No PIVH Who Were VLBW Infants

The mean GCI score on the McCarthy Scales of Children's Abilities of the 27 children with no PIVH was 97 (range, 75 to 123). Of the 25 children who were attending school, all were in regular classes. Two children were not yet enrolled in school.

The GCI score was within the normal range for 22 of the children (81%) and was borderline, ranging from 75 to 84, for five of the children. Nineteen children (70%) had normal age-related visuomotor integration skills, and 13 children (48%) had age-appropriate reading skills.

Children With PIVH Who Were VLBW Infants

The mean GCI score on the McCarthy Scales of Children's Abilities of the 11 children with PIVH was 95 (range, 71 to 120). All of the 10 children who were in school were in regular classes. One child was not yet enrolled in school. Seven of the children (64%) had normal GCI scores, and four children had borderline GCI scores, ranging from 71 to 83. Nine children (82%) had normal age-related visuomotor integration skills, and six children (55%) had age-appropriate reading skills.

Table 1.—Outcome Measurements for VLBW and Matched Control Children Born at Term*

	Term (n=22)	VLBW (n=38)	P
Postnatal age, mo	72.7 (60-85)	72.0 (60-84)	. . .
McCarthy Scales of Children's Ability	117 (89-141)	97 (71-123)	<.01
Test of Early Reading Ability	104.1 (79-139)	84.9 (55-126)	<.01
Developmental Test of Visual-Motor Integration	11.9 (9-16)	9.8 (4-15)	NS
Benton Finger Localization			<.01
R	9.2 (8-10)	7.5 (3-10)	
L	9.1 (7-10)	7.1 (3-10)	

*VLBW indicates very-low-birth-weight; NS, not significant. Values are mean (range).

Matched Control Preschool Children's Performance Outcome Results

The mean postnatal age of the children who were VLBW infants was 72.0 months (range, 60 to 84 months), and the mean age of the control children who were born at term was 72.7 months (range, 60 to 85 months). Means and ranges of outcome measurements for the two groups are given in Table 1. The mean scores for the control group were consistently better for all test measurements when compared with the VLBW group. Multivariate analysis demonstrated a significant difference between the groups for the four dependent variables combined ($P<.01$). On univariate analysis, a significant difference ($P<.05$) was noted on the McCarthy Scales of Children's Abilities, the Test of Early Reading Ability, and Benton Finger Localization. The mean GCI score for the control group was 117, compared with 97 for the children who were VLBW infants. Although the mean GCI score for the control group was significantly higher than that of the VLBW group (117 vs 97), both were in the normal range.

Comparison of VLBW Infants With and Without PIVH

Multivariate analysis demonstrated a significant difference between the children with no PIVH and the children with mild PIVH ($P<.05$) on the four test measures combined. On univariate analyses, the two groups of children did not differ significantly on any of the individual tests (Table 2).

COMMENT

Studies comparing school-age children who were VLBW infants with children who were term infants indicate that those in the VLBW group function less well on outcome measures of visuomotor and visual-perceptual function and have learning difficulties.[20-26] In spite of these problems, the majority of

Table 2.—Outcome Measurements for VLBW Children With and Without Grades I and II PIVH*

	PIVH (n=11)	No PIVH (n=27)	P
Postnatal age, mo	73.7 (62-84)	71.3 (60-83)	. . .
McCarthy Scales of Children's Ability	95 (71-120)	97 (75-123)	NS
Test of Early Reading Ability	90.8 (66-126)	82.6 (55-110)	NS
Developmental Test of Visual-Motor Integration	10.8 (5-15)	9.4 (4-15)	NS
Benton Finger Localization			NS
R	7.3 (3-10)	7.6 (5-10)	
L	7.1 (3-10)	7.0 (3-10)	

*VLBW indicates very-low-birth-weight; PIVH, periventricular, intraventricular hemorrhage; and NS, not significant. Values are mean (range).

these children are reported to be attending regular school.[25,26] Many, however, require remedial education.[24,26]

Since the VLBW cohort reported in most studies includes children with overt neurodevelopmental problems, the outcome data represent relative group trends. This may adversely bias the outcome of children with normal intelligence and no overt neurologic abnormality. Klein et al[25] compared the outcome of 46 neurodevelopmentally normal preschool children who were VLBW with a closely matched term group and found that the VLBW group had significantly poorer visuomotor and visual-perceptual function.

Few studies have tracked the neurodevelopmental outcome of children who were VLBW infants from infancy to school age. Vohr and Garcia-Coll[26] assessed a cohort of 22 7-year-olds who were neurologically normal at 1 year corrected age and found that 45% of the children had inefficient visuomotor skills and 9% had poor reading skills. Although none of the children required special education, six of the 22 were receiving remedial education.

In the present study, we have not only tracked longitudinally the neurodevelopmental outcome of children who were VLBW infants, but we have also compared their outcome with that of a closely matched cohort of children who were term infants. In addition, only children who were considered neurologically and developmentally normal at 1 and 2 years of adjusted age were included. Our results reflect those of Klein et al[25] and Vohr and Garcia-Coll.[26] The VLBW group scored significantly lower on a combined neuropsychological battery than did the term group. Specific deficits were in visual-perceptual and tactile-perceptual skills. Although the difference in visuomotor function was not significant, the VLBW group had more inefficient visuomotor skills. All of the children in the VLBW group were in regular classes. Since the majority of the children were in kindergarten or first grade at the time of the evaluation, the need for remedial instruction could not be assessed definitively. However, the poor performance of the children on tactile-perceptual, visuomotor, and visual-perceptual tests implies that they are at risk for learning difficulties.

While the neurodevelopmental outcome of school-age children who were VLBW infants has been evaluated extensively, there have been few reports that address the potential impact of brain injury, specifically PIVH, on the long-term neurodevelopmental outcome of these children.[9,11,12] Studies of preschool children who were VLBW infants and who had documented PIVH indicate that there is a direct relationship of moderate and severe PIVH and poor neurodevelopmental outcome.[9-11] The majority of the children in these studies exhibit neurologic sequelae with relative sparing of cognitive function. Although neurodevelopmental outcome studies of VLBW infants who incurred a mild PIVH suggest that mild PIVH does not increase the risk for neurodevelopmental sequelae in infancy, the number of children who have been tracked to preschool age is too small to determine what impact, if any, mild PIVH has on long-term outcome.[3,4,8-10,12]

We have demonstrated that children who were VLBW infants with mild PIVH and who were considered to be free of handicaps at 1 to 2 years of age do not fare as well as their counterparts with no PIVH at 5 to 6 years of age. The children with mild PIVH did not exhibit a significant difference on any single test but, rather, scored significantly lower on the combined neuropsychological battery. While the lower score of the children with mild PIVH on the combined battery suggests that PIVH amplifies the risk for poor school performance, additional neuropsychological assessment is necessary to substantiate this observation and to delineate specific problem areas.

In summary, the present study demonstrates that longitudinal neurodevelopmental assessment utilizing a neuropsychological battery is essential to measure the impact of VLBW and its attendant complications on ultimate performance. Children who were VLBW infants performed less well at 5 to 6 years of age than they did at 1 to 2 years of corrected age on neurodevelopmental testing. Specific deficits were noted in visual-perceptual, visuomotor, and tactile-perceptual skills, areas that cannot be assessed at 1 to 2 years of age. Moreover, although individual test scores for children with mild PIVH did not differ significantly from those of children with no PIVH, the significant difference in the combined test scores suggests that PIVH may have an adverse effect on global performance.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Apneic Oxygenation in Apnea Test for Brain Death: A Controlled Trial
Stephen A. Marks, MD, James Zisfein, MD (*Arch Neurol.* 1990;47:1066-1068)

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

The Probability of Obtaining Compatible Blood From Related Directed Donors
Michael H. Kanter, MD, Susan E. Hodge, DSc (*Arch Pathol Lab Med.* 1990;114:1015-1018)

Pulmonary Blastoma With Malignant Melanoma Component
Rosana E. Cohen, MD; Michael G. Weaver, MD; Hugo D. Montenegro, MD; Fadi W. Abdul-Karim, MD (*Arch Pathol Lab Med.* 1990;114:1076-1078)

Neonatal Intracranial Choriocarcinoma
Sunity Arya Chandra, MD; Enid F. Gilbert, MD; Chirane Viseskul, MD; Charles M. Strother, MD; Ray V. Haning, MD; Manucher J. Javid, MD (*Arch Pathol Lab Med.* 1990;114:1079-1082)

Percutaneous Central Venous Catheterization

Three Years' Experience in a Neonatal Intensive Care Unit

Mary Kay Chathas, RN, MSN; John B. Paton, MD; David E. Fisher, MD

• Prolonged venous access is desirable in very-low-birth-weight infants and infants for whom feedings are contraindicated. We prospectively evaluated 481 small-diameter venous catheters placed percutaneously in 317 patients over 3 years. Of 478 catheters, 241 (50%) were placed in infants weighing 1 kg or less. Mean catheter stay was 13 days (range, less than 1 to 77 days). Almost half (49%) of the central and thoracic catheters (91% of placements) were removed nonelectively: 43% due to problems such as leaking or clotting and 6% to suspicion of sepsis or venous occlusion. Of the 23 episodes of possible sepsis in the 478 catheter stays, six (1.3%) were confirmed catheter-related sepsis; 12 (2.5%) were confirmed alternate locus sepsis. Three factors specific to percutaneous central venous catheter-related sepsis were prolonged catheter stay (3 to 5 weeks), *Staphylococcus epidermidis*, and weight less than or equal to 1 kg. Four factors specific to alternate locus sepsis were presence of an alternate infection site, earlier infection (1 to 2 weeks), extremely low birth weight, and prolonged clinical instability. Percutaneous central venous catheterizations reduced the need for the stress of repeated venipuncture, resulting in lower complication rates than those reported with surgically placed central venous catheters, and leading to identification of risk factors specific to catheter sepsis and alternate locus sepsis.

(*AJDC.* 1990;144:1246-1250)

Use of percutaneous central venous catheters (PCVCs) as the primary means of maintaining vascular access in neonates has now been reported by neonatal practitioners in several studies with small series of patients.[1-5] This technique involves percutaneous placement of a small-diameter catheter into a peripheral vein for central passage. A major advantage includes bedside placement of PCVCs by skilled clinicians with minimal stress to the patient. Additionally, PCVCs can help reduce the iatrogenic stress of intensive care[6] by eliminating the need for repeated venipunctures, vein cut-downs, and extended use of umbilical artery catheters as access ports. The incidence of serious complications with PCVCs[1-5] is lower than those reported with surgically placed central venous catheters.[7-14]

We studied the frequency, origins, and associated risk factors for sepsis with the use of PCVCs in the largest series of patients known to us to be studied to date in a busy neonatal intensive care unit. The information obtained may assist in the development of a prospective management plan for PCVCs.

PATIENTS AND METHODS

Patient Population

All PCVCs were placed at bedside in the neonatal intensive care nursery at Michael Reese Hospital and Medical Center, Chicago, Ill, between November 1983 and October 1986. Patients considered candidates for placement of a PCVC included those with weight less than or equal to 1200 g or need for intravenous access for nutritive or nonnutritive purposes for at least 1 week. Decisions for catheter placement were made jointly by the nurses and physicians. Catheter insertions were performed by members of the nursing team who were certified following a structured educational program.[15]

Placement Technique

All PCVCs were 1.9F catheters (Silastic, Gesco International, San Antonio, Tex) inserted through a thin-walled, 20-gauge, breakaway butterfly needle. Each catheterization involved percutaneous insertion into a peripheral vein; venous cut-down was not necessary. Generally, veins in the arm (basilic, cephalic, and axillary) were considered optimal sites for insertion because they are easiest to access and comfortable for the patient. However, with very small infants (less than or equal to 750 g) and larger infants (greater than or equal to 2500 g), percutaneous access to arm veins was more difficult due to vein size and depth. In these neonates, external jugular or temporal veins were often used as insertion sites.

A chest roentgenogram was obtained following placement to verify tip location. Preferable tip locations included the right atrium or superior vena cava. Other acceptable tip locations included thoracic placement between the superior vena cava and axillary vein, and peripheral placement in femoral, cephalic, or temporal veins. Tip placements in a peripheral vein were either by choice if the neonate had positive blood cultures and central placement was pending a negative set of cultures, or due to difficulty with catheter advancement.

Maintenance Techniques

Percutaneous central venous catheters were used exclusively for hyperalimentation or administration of intralipids or dextrose solutions. A few critically ill patients with fluid and/or electrolyte imbalances often required a second access for infusion of blood products and/or volume expanders. In these instances, a second peripheral or thoracic PCVC was inserted and used for the limited time needed for volume infusions.

Medications were given via PCVCs by either direct injection or continuous infusion through a Y-port in the administration set. The initial dressing was only changed when nonocclusive or restrictive.[15] Specific protocols were followed by nursing staff for medication administration, as well as for additional care components such as dressing change, blunt-end luer insertion, intralipid infusion, blood culture sampling, and PCVC removal.[15]

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From the Michael Reese Hospital and Medical Center, Chicago, Ill, and the University of Illinois at Chicago.

Reprint requests to Department of Pediatrics 12-KC, Michael Reese Hospital and Medical Center, Lake Shore Dr at 31st St, Chicago, IL 60616 (Dr Chathas).

Cultures

Aseptic technique was adhered to during catheter removal and while securing and sending catheter tips for culture. Cultures were obtained on 71% of the catheters placed, with an increasing proportion each study year (from 57% in the first year to 78% in the last 2 years) as compliance and technical issues became less problematic. In light of research findings implicating the hub as a possible origin of colonization,[16] hub cultures were also obtained on those catheters left in place for 14 days or longer during the last year of the study. Blood cultures were obtained if the neonate showed signs of sepsis, including any one or more of the following: bradycardia, hypothermia, circulatory changes, feeding intolerance, and lethargy. If possible, blood cultures were drawn through the catheter; if catheter return flow was inadequate for sampling, cultures were then obtained through a peripheral venipuncture. Cultures of endotracheal aspirate, skin, cerebrospinal fluid, stoma, or stool were obtained when other sites of possible infection were identified.

Differentiation of PCVC-related sepsis and sepsis related to an alternate locus was in accordance with definitions from previous research identifying the origin of infection in patients with central catheters.[9,17-22] Percutaneous central venous catheterization–related sepsis episodes are based on the following definition of catheter-related sepsis: catheter tip/hub and blood culture yielding the same organism, along with clinical symptoms of sepsis, for which no anatomic locus other than the catheter could be identified.[22] Sepsis related to an alternate locus was defined by a positive endotracheal, skin, wound, stoma, or stool culture that temporally preceded a positive blood culture and was accompanied by clinical symptoms of local infection and general sepsis.[8,17-22] Bacteremia was defined by one or more positive blood cultures in an asymptomatic patient.[9,22]

Data Collection

A standardized record was completed prospectively for each catheterization. Information collected included clinical presentation at insertion, daily status, rationale for removal, and blood and catheter tip/hub culture results.

Microbiologic surveillance and documentation were initiated if patients either had clinical signs of sepsis or showed evidence of either a positive blood culture or a positive culture from an alternate infectious site. A standardized data collection tool was prospectively developed for this purpose, using data from multiple sources. Maintenance of this record allowed for temporal distinction between catheter-related sepsis and sepsis related to an alternate locus. Data management and analysis were performed using SAS computer programs (SAS Institute, Cary, NC) as specified below.[23]

RESULTS

Demographics

From November 1983 to October 1986, 481 PCVC catheters were placed in 320 infants for a total of 6206 catheter days. Data for three PCVC stays were unavailable for follow-up because the infants were transferred back to their referral hospital. The study sample is described in Table 1. Infants' weights at catheter placement are described in Table 2. The number of PCVCs required per hospital stay for each patient, including all catheters placed (right atrial and superior vena caval and in thoracic and peripheral tip locations), is described below:

	No. of Catheters	No. (%) of Patients
	1	224 (70.7)
	2	53 (16.7)
	3	26 (8.2)
	4	8 (2.5)
	5	5 (1.6)
	13	1 (0.3)
Total	478	317 (100)

Successful right atrial or superior vena caval placement occurred in 78% of PCVCs. Another 13% were thoracic tip placements, while 9% were peripheral. Mean time in place for catheters removed electively was 14.3 days, and for those removed nonelectively, 12.6 days.

Rationales for Removal

Rationales for removal of central and thoracic catheters in 436 patients are described below:

Rationale	No. (%) of Patients
Nonelective	
Clotting	101 (23.2)
Leaking	44 (10.0)
Contaminated	23 (5.3)
Presumed sepsis	21 (4.8)
Edema	12 (2.8)
Venous occlusion	7 (1.6)
Other	8 (1.8)
Total	216 (49.5)
Elective	
Full feedings	179 (41.1)
Death due to unrelated causes	34 (7.8)
Extended placement	7 (1.6)
Total	220 (50.5)

Table 1.—Demographics (N = 478)

	Mean ± SD	Range
Birth weight, g	1219.65 ± 662.59	450-4320
Insertion weight, g	1273.06 ± 719.63	440-4280
Gestational age, wk	29.90 ± 3.93	24-41
Days in place	12.98 ± 10.82	<1-77

Table 2.—Catheter Days in Place by Infants' Weight at Percutaneous Central Venous Catheter Insertion

Weight, g	No. (%)	Mean Days in Place (Range)
≤750	91 (19.0)	16.27 (<1-59.0)
751-1000	150 (31.4)	14.77 (<1-55.0)
1001-1500	140 (29.3)	12.18 (<1-77.0)
>1500	97 (20.3)	8.30 (<1-42.0)

Catheters with peripheral tip locations (43.0 [9%] of 478) were excluded from this analysis, because tip location in a small-diameter peripheral vein represents a different circumstance from that of tip location in a high-flow, large-diameter central vessel. Of the 21 (5%) catheters removed for "presumed sepsis," 5 (24%) were actually sepsis free, as determined by follow-up or concomitant negative blood and tip culture results.

Incidence of Sepsis

Of the 478 catheter stays, there were 23 cases of possible sepsis. After review of each case of possible sepsis, incidence of PCVC-related sepsis was found to be 1.3% (six confirmed cases), and incidence of sepsis related to an alternate locus was 2.5% (12 confirmed cases). A description of findings from each group follows.

PCVC-Related Sepsis.—Eight positive blood cultures were related to the catheter, with all other sources of possible infection ruled out. Of the eight positive blood cultures, six were sepsis episodes confirmed by the presence of clinical signs of sepsis, and blood and catheter cultures (tip or hub) positive for the same organism. In the two unconfirmed cases, neither neonate showed any clinical signs of sepsis, but both had blood and catheter tip cultures positive for the same organism. Blood cultures were obtained in the absence of clinical signs because the infants were known to be heavily colonized at alternate sites.

Alternate Loci–Related Sepsis.—Twelve cases of sepsis were related to infectious sites other than the PCVC.

Asymptomatic Bacteremia.—Clinical signs of sepsis and all blood, alternate loci, and catheter tip cultures were reviewed for each of the 23 cases of possible sepsis. Three cases were considered false-positive and unrelated to sepsis. In each, blood cultures were positive, but infants were asymptomatic and tip/hub cultures were negative.

Risk Factors Identified in Cases of PCVC-Related Sepsis.—Of the six confirmed PCVC-related sepsis episodes, five appeared to be related to prolonged catheter stay, ranging from 21 to 39 days. The one other case was associated with marked fluid restriction and thrombus formation.

Risk Factors Identified in Cases of Sepsis From Alternate Loci.—In the 12 cases of sepsis due to alternate loci, there was variability in the originating sites of infection, the patients' weights, the clinical diagnoses and complications, and the causative organisms. Sources of infection are identified as follows: of the 18 confirmed cases of sepsis, 12 were alternate locus–related and six were PCVC-related. The sources of positive culture in cases with alternate locus–related sepsis were as follows:

Source	No. of Patients
Multiple sites	4
Respiratory tract	2
Umbilical artery catheter	2
Necrotizing enterocolitis	1
Skin	1
Wound	1
Eye	1

Associated findings in cases of PCVC-related sepsis were as follows: placement less than 21 days, five patients; thrombus and low blood volume, one patient.

Six of the 12 infants with sepsis due to alternate loci weighed less than 750 g, five weighed between 750 and 1200 g, and one weighed 3320 g at PCVC insertion. The onset of infection varied: positive blood cultures were obtained within the first week after placement in two cases, within the second week in seven cases, and within the third week in three cases of sepsis. By comparison, the onset of infection in the group with alternate loci-related sepsis occurred much earlier (majority by week 2) than in the group with PCVC-related sepsis (all between 3 and 5 weeks).

In contrast to findings with PCVC-related sepsis, organisms from this group with sepsis due to alternate loci were varied, including both skin and enteric flora. Single organism pathogens identified were *Staphylococcus epidermidis*, *Candida albicans*, *Serratia marcescens*, and *Enterococcus*. In three of the 12, two organisms were isolated from blood cultures; in each, *S epidermidis* was one of the organisms.

By comparison, patients with sepsis related to an alternate locus showed less favorable clinical conditions during catheter stay than did patients with PCVC-related sepsis. Compromised skin integrity resulting in an overwhelming *S epidermidis* sepsis represented the most extreme case among the 12 cases of alternate loci–related sepsis. Two other risk factors in addition to compromised skin integrity were identified on case study review: prolonged ventilatory support and concurrent use of umbilical artery catheter (UAC) and PCVC for particularly small, unstable infants were noted in one case of candidiasis and two cases of *S epidermidis* sepsis. Frequent sampling from the UAC, coupled with additional clinical risk factors of skin sloughing, dexamethasone sodium phosphate use, and repeated hypoxia resulted in UAC-associated infections and hematogenous seeding in these three neonates. In the one case of candidiasis, hematogenous seeding from a UAC was the presumed cause of abdominal wall cellulitis and multiple organ involvement with the *Candida albicans* identified on autopsy.

Relative Risks of PCVC and Alternate Locus–Related Sepsis

The associations between potential risk factors cited in the literature[24] and PCVC and alternate loci-related sepsis were determined using the Cochran-Mantel-Haenszel summary relative risk estimate (Table 3).[25,26]

Trend Test for Dose Response

Our colonization rate for those catheter tips cultured was 20%. A dose-response analysis to demonstrate a continuously increasing relative risk of colonization with increasing exposure to time was performed[27]; the resulting test for trend was significant with $\chi^2 = 8.43$ (1 *df*).

COMMENT

The use of PCVCs in our neonatal intensive care unit has helped avoid the compromising cycle of peripheral intra-

Table 3.—Relative Risk of Sepsis

	Estimates of Relative Risks (95% Confidence Intervals)*		
Risk Factors	PCVC-Related	Other-Related	Both
Skin abrasions	2.08 (0.26, 16.77)	10.38†(4.23, 25.52)	6.61†(2.95, 14.78)
PCVC stay, >21 d	8.86†(2.20, 35.76)	1.48 (0.41, 5.33)	2.82†(1.16, 6.87)
Weight, <1.0 kg at PCVC insertion	5.44 (0.81, 36.37)	11.96†(2.45, 58.32)	8.70†(2.63, 28.77)
Weight, <750 g at PCVC insertion	2.19 (0.42, 11.34)	6.12†(2.27, 16.52)	4.38†(1.91, 10.02)
Age, <30 wk at PCVC insertion	4.05 (0.57, 29.09)	4.05†(1.02, 16.19)	4.05†(1.32, 12.46)
Surgery	1.06 (0.13, 8.95)	1.06 (0.24, 4.74)	1.06 (0.31, 3.57)
Mechanical ventilation	1.73 (0.21, 14.28)	0.69 (0.21, 2.25)	0.90 (0.33, 2.48)
Difficult insertion	0.27 (0.04, 2.01)	1.37 (0.45, 4.16)	0.87 (0.34, 2.20)
Dressing changes (one or more)	0.72 (0.09, 6.03)	0.33 (0.05, 2.23)	0.45 (0.11, 1.83)

*Determined with Cochran-Mantel-Haenszel summary statistics. PCVC indicates percutaneous central venous catheter.

†Significant relative risk does not include unity.

venous access well known to all who work in neonatal intensive care units.[6] Our initial experiences with PCVCs were positive—catheter placement proved to be a relatively quick bedside procedure, provided the appropriate vein site was selected for the individual patient; consistency in catheter maintenance was achieved through the use of standard protocols. Our data demonstrate that PCVCs provide a safe means of maintaining long-term venous access for neonates compared with a surgical approach.[7] Of all the catheters placed, 51% were removed electively and 43% were removed for minor mechanical problems such as leaking and clotting. Mean time in place for catheters electively removed (14.3 days) and for those nonelectively removed (12.6 days) were similar, so that clinical benefit was achieved with those catheters removed nonelectively.

Presumption of sepsis accounted for 5% of the nonelective removals. Within this group, six cases were confirmed episodes of PCVC-related sepsis, 12 were confirmed episodes of sepsis related to an alternate locus, and five were related to another clinical problem that mimicked sepsis and led to catheter removal. The rate of PCVC-associated episodes of sepsis (1.03 episodes per 1000 catheter days) in this study was lower than crude rates of catheter-related sepsis reported in other patient populations.[28,29] The incidence of sepsis related to another source of infection was low as well (1.93 episodes per 1000 catheter days). This is especially important because of the large number of low-birth-weight infants in our cohort. Of the 478 catheters inserted, 92 (19%) were placed in infants weighing less than or equal to 750 g, and 150 (31%) were placed in infants 751 g to 1 kg. Low birth weight is associated with problems that can heighten sepsis risk, including feeding intolerance, prolonged ventilatory support, intracranial hemorrhage, and skin abrasions.

Review of cases of possible sepsis in our cohort resulted in the identification of the following three factors associated with PCVC-related sepsis: prolonged catheter stay (3 to 5 weeks), colonization with *S epidermidis*, and low birth weight (less than or equal to 1 kg). This suggests that skin flora and time are positively correlated with catheter sepsis, and removal of a PCVC during week 4 would reduce this risk.

Four factors were identified in the 12 cases of sepsis not related to the PCVC—either single (75%) or multiple (25%) organism colonization at alternate sites with skin and enteric flora, accompanied by signs of local infection, very low birth weight (50% less than or equal to 750 g), prolonged clinical instability, and an earlier onset of infection (generally by week 2). Among the neonates with prolonged clinical instability, three characteristics appeared significant—compromised skin integrity, prolonged ventilatory support, and long-term concurrent use of UAC and PCVC. On the basis of our data from the 12 cases of alternate loci sepsis, we suggest that periodic culturing (eg, weekly) of possible infection sites and of blood in neonates with any of the above characteristics could serve to promote risk reduction. In contrast to management of patients with PCVC-related sepsis, limiting the length of catheter stay with early removal and replacement may not be the most appropriate solution for patients with heavily colonized loci for infection. Instead, retention of the catheter for delivery of antibiotics or antifungal medications to clear a bacteremia or fungemia identified with surveillance cultures may be a more practical solution.

Prospective data collected from our cohort on risk factors for sepsis cited in the literature were used to determine relative risks of sepsis. The resulting significant relative risks support previous research findings that time, skin integrity, and low weight can increase sepsis risk in patients with central lines.[30,31] Results of the dose-response test for colonization trend over time show a significant test statistic, confirming the dose-response relationship between increasing duration of catheter stay and catheter colonization. Reduction of catheter colonization by limiting catheter stay should reduce the risk of PCVC-related sepsis.

In summary, use of PCVCs has proven beneficial in our high-risk patient group, and has resulted in comparatively low rates of sepsis.[7-14] Although early studies of central line use and total parenteral nutrition emphasized only catheter-related sepsis hazards, a number of recent studies have addressed the issue of distinguishing between sepsis related to an alternate locus and sepsis related to the catheter, and have attempted to identify the differential predicting factors for each group.[9,17-22] We also feel that distinguishing between these two types of sepsis is an important step, because surveillance plans and catheter management for each group may differ. Our study indicates that there is a need for additional research to predict risk of colonization and sepsis. Development of statistical models to predict risk of PCVC-related and alternate locus-related sepsis are needed to determine which are the most significant predictors of sepsis. Cohort studies addressing the issues of length of safe catheter stay, frequency of blood and alternate site culturing, concurrent use of multiple lines, catheter manipulations necessary per PCVC stay (eg, dressing change, medication administration, and heparin sodium additives), and administration of immunoglobulin to patients with high risk of sepsis are needed to support maintenance care of PCVCs.

Based on our study, we are able to draw the following conclusions concerning patients with PCVCs: neonates without alternate infection sites identified should have weekly blood cultures drawn and catheters removed by week 4; neonates with alternate sites of infection should have blood and site cultures done weekly or more often if necessary; treatment through the catheter to clear a bacteremia in these patients may be more appropriate than removal before 4 weeks. Studies are now being carried out to develop high-risk profiles for colonization and sepsis through multifactorial analysis, and to determine the optimal heparin delivery method and dose effective in reducing clotting.

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Additional clinical information on cases of sepsis in tabled form is available from the authors on request.

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Book Review

Fetal, Neonatal and Infant Cardiac Disease, edited by James H. Moller and William A. Neal, 1034 pp, with illus, $180, East Norwalk, Conn, Appleton & Lange, 1990.

As the scope and complexity of pediatric cardiology have expanded during the past decade, encompassing in a single text the accumulated information about this field has become more diffficult. The editors of this reference-style book have succeeded in bringing together an exceptional group of collaborators to compile a well-focused text on children with cardiac disease. Since the ultimate outcome of congenital heart disease is often determined by the earliest management decisions, this focus is well placed.

The first section explores the scientific foundations of our understanding of structure and function in the developing heart. The chapters on growth, morphogenesis, and function tie the most advanced theory of gene control to familiar congenital defects. Subsequent chapters on the conduction system, myocardium, and pulmonary and systemic circulations maintain this high level of integration of the new with the previously understood. The section on diagnostic methods goes far beyond the usual fare to explore the physics, basic physiology, diagnostic theory, and practical applications of each technique. Section III is composed of 23 chapters dealing with major diagnostic categories. These subjects are treated with rich detail, offering a wealth of information in a style that is easily understood by those outside the field. The same can be said of the following section on acquired cardiac conditions. A final section on management considerations includes excellent chapters on perioperative management and offers a comprehensive look at the special problems of the infant: congestive failure, shock, metabolic imbalance, nutrition, and ventilatory care.

While writing this review, I frequently delved into this text to prepare lectures for students, residents, and cardiologists. Its well-thumbed appearance is probably the best indicator of usefulness. On every subject there is new and fresh material presented with excellent graphic material. This book addresses the major themes of modern pediatric cardiology with a depth and clarity that make it useful for trainees at all levels, experienced clinicians, and teachers.

ROBERTA G. WILLIAMS, MD
University of California
Department of Pediatrics
Division of Cardiology
UCLA Medical Center
Los Angeles, CA 90024

Physical Features of Prader-Willi Syndrome in Neonates

David J. Aughton, MD, Suzanne B. Cassidy, MD

• A retrospective study of 16 patients was undertaken to identify physical features that may typify neonates with Prader-Willi syndrome. Several features known to be typical of Prader-Willi syndrome in early infancy were confirmed, including hypotonia and genital hypoplasia. A number of features that have not previously been emphasized as characterizing Prader-Willi syndrome were also identified, most notably abnormal cry and, in males, signs of genital hypoplasia but with an apparently normal phallus. Other features included disproportionately large head circumference, disproportionately large anterior fontanelle, mild micrognathia, mild anomalies of the gingivae or alveolar ridges, and changes in the appearance of the skin. Appreciation of these features may assist the pediatrician in recognizing the child with Prader-Willi syndrome during the neonatal period, before the appearance of better-known findings of later onset, such as obesity and acromicria.

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Prader-Willi syndrome (PWS) is a usually sporadic, multisystem disorder that is characterized after infancy by obesity, acromicria (small hands and feet), short stature, hypogonadism, and abnormal cognitive and behavioral functioning. Subtle but distinctive dysmorphic facial features include a narrow bifrontal diameter, "almond-shaped" palpebral fissures, and a thin, downturned upper lip.[1,2] Deletion or some other anomaly involving the proximal portion of the long arm of chromosome 15 is demonstrable, with the use of high-resolution cytogenetic techniques, in about 60% of cases.[3-5] In infants, PWS is often difficult to diagnose because the clinical picture differs from that seen later in life. Infants exhibit hypotonia, genital hypoplasia, and feeding problems, with "failure to thrive." Although, in some cases, dysmorphism may be observed in the neonatal period,[6,7] more commonly dysmorphic features are subtle or absent.

Early diagnosis of this condition may have a positive impact on its natural history.[8] The present study was conducted in an effort to identify physical features that may typify PWS in the neonatal period and thereby potentially improve the rate of early diagnosis.

PATIENTS AND METHODS

Medical records of all patients who were observed in the PWS clinic at the University of Connecticut Health Center, Farmington, were reviewed for descriptions made during the newborn period (ie, ≤1 month of age). Sixty-one charts were available for review; in 17, a record of a physical examination performed during the first month of life was present. One patient had features atypical of PWS and was excluded; the remaining 16 patients all had "typical" PWS features and conformed to previously described diagnostic characteristics.[2]

Records were reviewed for information concerning mode of delivery, presentation at birth, Apgar scores, birth measurements (length, weight, and head circumference), size of anterior fontanelle, and gestational age. The specialty of the examining physician was noted, as was any reference made to PWS in the initial differential diagnosis. Descriptions of neonatal examinations were reviewed for abnormal findings.

Birth measurements or, when initial examination was not performed at birth, measurements at the time of initial examination were plotted against the standards of Babson and Benda.[9] Anterior fontanelle sizes were plotted against the standards of Davies et al.[10] Measurements were expressed as SDs above or below the mean for age.

The results of previously obtained high-resolution cytogenetic studies were recorded.

RESULTS

The 16 patients consisted of 11 males and five females. At the time of the chart review, the patients ranged in age from 8 months to 33 years (average age, 9.6 years). All initial examinations were performed at 22 days of age or earlier; 11 were done within the first week of life, and nine were conducted within the first 2 days of life. Three examinations were conducted by pediatricians; five were done by clinical geneticists; five were performed by pediatric neurologists (with an examination by a pediatrician also recorded for two of the five); and one was done by a neonatologist. In two patients, the specialty of the examining physician was not recorded. Gestational age ranged from 32 to 42 weeks (and was described simply as "term" in three patients), and it was not recorded in one patient; the average of the 12 specific gestational ages recorded was 38 weeks. Birth weights ranged from 2000 to 4010 g, with an average of 2920 g. Breech presentation was noted in three (19%) of the 16 patients. Delivery was accomplished by cesarean section in seven (44%) of the 16 patients. Apgar scores were recorded for 12 patients; the average scores were 6 at 1 minute (range, 1 through 8) and 8 at 5 minutes (range, 4 through 9).

Two patients were born before the original description of PWS.[1] Of the remaining 14 patients, PWS was considered in the differential diagnosis in only three; in each patient, the examiner was a geneticist. The diagnosis was considered in an additional patient at 10 weeks of age during a follow-up visit with a pediatric neurologist.

Thirteen (81%) of the 16 patients had undergone high-resolution chromosome

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From the Department of Pediatrics, Division of Genetics, William Beaumont Hospital, Royal Oak, Mich (Dr Aughton), and the Section of Genetics/Dysmorphology, Department of Pediatrics and The Children's Research Center, The University of Arizona, Tucson (Dr Cassidy).

Presented in part at the Ninth Annual David W. Smith Workshop on Malformations and Morphogenesis, Oakland, Calif, August 5, 1988.

Reprint requests to Department of Pediatrics, Division of Genetics, William Beaumont Hospital, 3601 W Thirteen Mile Rd, Royal Oak, MI 48073 (Dr Aughton).

Findings in 16 Neonates With PWS*

Finding	No. With Finding Present/ No. With Finding Mentioned†	
Previously described		
Neurologic		
Hypotonia	16/16	
Diminished DTRs	9/14	
Brisk DTRs	1/14	
Craniofacial		
Unusual palpebral fissures‡	5/6	
Unusual forehead§	4/4	
Unusual mouth‖	3/4	
High-arched palate	3/4	
Skeletal		
Small hands	1/3	
Small feet	0/3	
Genital		
Cryptorchidism	9/10	(n=11)
Scrotal hypoplasia	7/9	(n=11)
Genital hypoplasia (female)	1/2	(n=5)
Not previously emphasized		
Neurologic		
Unusual cry¶	13/13	
Craniofacial		
Unusual pinnae#	5/11	
Small mandible	4/4	
Unusual gingivae**	3/4	
Unusual nose††	2/2	
Skeletal		
Small-joint laxity	2/3	
Clinodactyly	2/5	
Long and/or tapering fingers	2/5	
Genital		
Apparently normal penis	7/7	(n=11)
Skin		
"Poor color"	5/6	
Cyanosis	4/5	
Jaundice	4/5	
Ecchymoses	4/6	
Hirsutism	3/3	
Pedal edema	3/4	
Simian crease	2/4	
Anthropometric		
HC>weight	12/13	
AF>HC	4/5	

*PWS indicates Prader-Willi syndrome; DTRs, deep tendon reflexes; HC, head circumference for age; weight, weight for age; and AF, anterior fontanelle size for age.

†The denominator includes all patients in whom the finding was present or noted to be absent; it excludes those in whom the presence or absence of the finding was not addressed.

‡Small, upslanting, almond shaped, narrow.

§Frontal bossing, "short."

‖"Small, thin upper lip," "downturned, triangular," small.

¶Weak, stridorous, high pitched, "not sustained," "squeaky."

#Low set, "malformed," small, "poor cartilage," prominent.

**Accentuated, anterior sloping, "generous alveolar ridge."

††Small, beaked, prominent, upturning.

analysis at some time during their lives. All but one of these patients showed the typical deletion of the long arm of chromosome 15; the other patient had normal chromosomes.

The Table summarizes the physical features noted in two or more infants with PWS. In the top part of the Table are listed those features that have previously been emphasized as being associated with PWS (whether or not in the neonatal period). In the bottom part of the Table are listed the features that have not before been emphasized as being associated with PWS.

In 13 of the 16 patients, both the head circumference for age and the weight for age were recorded. In 12 (92%) of the 13 patients, the head circumference for age exceeded the weight for age (although true macrocephaly, ie, head circumference for age in excess of 2 SDs above the mean, was present in only two patients); in the remaining patient, the head circumference for age was slightly less than the weight for age.

In five of the 16 patients, both the anterior fontanelle size for age and the head circumference for age were recorded. In four (80%) of the five patients, the anterior fontanelle size for age exceeded the head circumference for age; in three of the four patients, the size of the anterior fontanelle was well in excess of 2 SDs above the mean. In the remaining patient, the anterior fontanelle size was average for age, while the head circumference for age was in excess of 2 SDs above the mean.

The following mild anomalies were commented on in single examinations only: boxlike cranium, Brushfield's spots, doughy muscles, Epstein's pearl, eyelid edema, flat philtrum, flexed hands and wrists, foot deformity, hemangioma, overlap of the second and third toes, puffy face, redundant knee tissue, sacral dimple, skin reactive to touch and "blotchy," soft skin, tight large joints, and unusual leg posture.

COMMENT

The physical features of adults with PWS are distinctive, and although strict diagnostic criteria for the condition do not exist, recognition of PWS in older children and in adults is relatively readily accomplished by those familiar with the disorder. Infants with PWS have proved to be difficult to recognize, however, and the diagnosis of this condition is often delayed until later childhood or even adulthood.

Ideally, investigations into the subtleties of the dysmorphic features of infants with PWS would be prospective in nature. However, prospective investigations require that infants with PWS can reliably be recognized at or very shortly after birth. At this time, this ability is limited at best, and the intent of retrospective studies, such as the present study, is to enhance this ability and thus provide a foundation for later prospective study.

Until recently, clinical recognition of infants with PWS has relied solely on the nonspecific signs of hypotonia, genital hypoplasia, and feeding problems. Stephenson[6] examined eight patients and stated that the face of infants with PWS is sufficiently distinctive to be of diagnostic value, but did not specifically characterize the dysmorphism beyond noting "slit eyes" and "down-curved slit mouth." Brisk deep tendon reflexes were also considered a characteristic finding. Greenberg et al,[8] examining five patients during the first 3 months of life, also emphasized short palpebral fissures and small mouth, as well as the diagnostic value of a narrow bifrontal diameter in these infants. They also noted that small hands and feet were not present at birth in infants for whom hand and foot measurements were available. Chitayat et al[11] studied four infants with PWS during the first year of life and emphasized additional features, including high forehead with frontal bossing, almond-shaped eyes with epicanthal folds, malar hypoplasia, high-arched palate, and minimal facial expression.

A number of previously recognized features of PWS in infancy were confirmed in the present study (Table, top part). Hypotonia was noted in all patients. The 19% prevalence of breech presentation among our patients compares favorably with the 22% reported by Holm,[2] and the increased rate of cesarean section seen in our population has also been noted previously.[12] Contrary to the findings of Stephenson,[6] but in accord with other observations,[13] diminution or absence of deep tendon reflexes was the rule among our patients; in only one patient were the deep tendon reflexes described as "brisk." Facial dysmorphism was noted infrequently; however, when noted, it often included an unusual appearance to the palpebral fissures, forehead, mouth, or palate.

Only one of five female infants was judged to have genital hypoplasia; this determination was made by one of the authors (S.B.C.) in an infant in whom the diagnosis was suspected at birth. Although it is possible that some female infants with PWS may have normal external genitalia at birth, it is much more likely that genital hypoplasia (small clitoris and/or labia minora) is present but unrecognized.

The commonness of genital hypoplasia among male infants with PWS was confirmed. Genital examinations were recorded for 10 of the 11 male patients; in only one patient were the penis, testes, and scrotum all judged to be normal. The remaining nine males all had cryptorchidism, scrotal hypoplasia, or both.

The hands and feet were specifically commented on in but three patients and were described simply as "normal" in two of these. In the third patient, the hands were measured and were of normal size; the feet were said to "appear small," but no measurement was recorded. These findings suggest that the hands and feet of infants with PWS are not usually sufficiently distinctive in appearance as to prompt measurement, and support previous observations that the hands and feet of neonates with PWS are of normal size.[8,11]

Several features not previously emphasized as being associated with PWS emerged (Table, bottom part). The quality of cry was commented on in 13 of 16 patients, and in all 13, the cry was abnormal. Although feeble cry has been noted previously,[2,11] it appears that unusual cry may provide a more important diagnostic clue than has been thought in the past.

Mild anomalies of the ears, mandible, nose, and gingivae and alveolar ridges were noted in some patients, as were subtle abnormalities of the hands and small joints. "Inward obliquity of the gums and retrognathia" were observed in one patient of Chitayat et al.[11] A variety of changes in the appearance of the skin were noted, most commonly cyanosis, jaundice, and "poor color." Chitayat et al[11] also noted "skin mottling" in their four patients, and changes in the appearance of the skin may represent a fairly consistent, albeit heterogeneous and nonspecific, finding among infants with PWS.

Although Stephenson[6] observed that "the penis was small but could never be described as tiny" among male infants with PWS, micropenis is more often considered a common feature of the disorder.[8] However, the size of the penis was commented on in seven of the 11 examinations performed on males in this study; in all seven patients, the penis was judged to be normal. Although normal measurements of stretched penile length for infants are readily available,[14] such measurements were recorded in none of our patients, and have been recorded in very few patients in the literature. Measurement of the stretched penile length is rarely ascertained routinely; such measurement is instead usually prompted by the examiner's subjective impression of abnormal penis size. It seems extremely unlikely that the paucity of reports in the literature of stretched penile length among male infants with PWS reflects some systematic inattention on the part of examiners; this paucity is much better explained as owing to an apparently normal size of the penis of these neonates (which would not, then, be expected to prompt measurement), and, hence, may be considered consistent with the findings of the present study. Thus, although genital hypoplasia is almost invariably present as cryptorchidism and/or scrotal hypoplasia in males with PWS, it appears that such hypoplasia infrequently manifests as micropenis.

Two anthropometric anomalies were also seen frequently (Table). In 12 of the 13 patients in which sufficient data were available to permit comparison of the head circumference for age with the weight for age, the head circumference for age exceeded the weight for age, suggesting that the head may be disproportionately large in infants with PWS. Furthermore, in four of the five patients in whom sufficient data were available to permit comparison of the anterior fontanelle size for age with the head circumference for age, the anterior fontanelle size for age exceeded the head circumference for age, suggesting that the anterior fontanelle may also be disproportionately large in infants with PWS. In comparison, the head circumference for age exceeded the weight for age at birth in one patient of Chitayat et al[11] and was in proportion to the weight for age in three; interestingly, one of the patients in the study of Chitayat et al[11] was also described as having a large fontanelle, and another was described as having a third fontanelle. The numbers of patients studied thus far are relatively small, and further investigation will be helpful in determining the precise value of a disproportionately large head circumference and/or a disproportionately large anterior fontanelle in diagnosing PWS in infancy. Nevertheless, it appears that these features characterize at least some infants with this condition and may be helpful diagnostically.

Finally, a variety of mild anomalies were commented on in single physical examinations only. The significance of these anomalies is unclear, and at least, they do not appear to typify PWS in infancy; whether any may represent an infrequent characteristic of PWS remains to be determined.

Recognition of PWS in the newborn period still relies primarily on observation of hypotonia, genital hypoplasia, and feeding difficulties, and the results of this study confirm that there are apparently fewer distinctive features of newborns with PWS than of newborns with most other dysmorphic conditions. Nevertheless, the findings from this and other studies suggest that a subtle but definite and recognizable constellation of dysmorphic features is present in many infants with PWS; appreciation of these features may assist the pediatrician in recognizing the infant with PWS. This constellation may commonly include a disproportionately large head circumference for weight, a disproportionately large anterior fontanelle for head circumference, mild micrognathia, unusual gingivae, changes in the appearance of the skin, and, in males, cryptorchidism and/or scrotal hypoplasia with an apparently normal phallus, and this constellation may often be accompanied by abnormal cry.

This work was conducted in part at the Department of Pediatrics, University of Connecticut School of Medicine, Farmington.

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Koichiro Shimamura, MD; Hideo Shigemi, MD; Yuichi Kurono, MD; Goro Mogi, MD (*Arch Otolaryngol Head Neck Surg.* 1990;116:1143-1146)

Transtympanic Endoscopic Findings in Patients With Otitis Media With Effusion

Haruo Takahashi, MD; Iwao Honjo, MD, DMSc; Akihiko Fujita, MD; Kyosuke Kurata, MD (*Arch Otolaryngol Head Neck Surg.* 1990;116:1186-1189)

Sports Medicine

William B. Strong, MD, Augusta, Ga
Carl L. Stanitski, MD, Pittsburgh, Pa
Ronald E. Smith, PhD, Seattle, Wash
Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*Have you ever been asked about a child's fitness for exercise? This review outlines the cardiovascular responses of children that differ from those known for adults. Gender, age, ethnicity, and other factors influence these responses and are clearly described in this article. Because Dr Strong is a co-author, I had the article independently reviewed and evaluated for inclusion in this section.*—V.A.F.

Cardiovascular Responses to Exercise in Childhood

David S. Braden, MD, William B. Strong, MD

• **We reviewed the normal cardiovascular responses to dynamic and static exercise in children and compared children's responses with those of adults and to expected responses to such training.**

(*AJDC.* 1990;144:1255-1260)

Pediatricians are frequently being asked to answer questions about children's exercise or physical fitness. Because of the increasing awareness and concern of parents, it is important for physicians to understand the normal cardiovascular response to exercise. Differences in size, exercise efficiency, and energy expenditure result in cardiovascular responses that may differ from adult responses.[1-3] Herein, we describe the cardiovascular responses to exercise in children and identify those areas in which children differ from adults.

Tables 1 and 2 present commonly used exercise terms and their definitions.[4,5]

Exercise increases the energy expenditure of the body. This energy expenditure is measured by the amount of oxygen consumed ($\dot{V}O_2$). Therefore, the $\dot{V}O_2$ is a measure of the intensity of the exercise that may be either *dynamic* (aerobic) or *static* (isometric). As the intensity of exercise increases, $\dot{V}O_2$ increases linearly in parallel until it plateaus. However, some trained individuals can continue to exercise at higher levels of intensity past the plateau in $\dot{V}O_2$.

To supply oxygen to exercising tissues, the body must have an intake system, a delivery system, and a carrying system. The respiratory system functions as the intake system, and for the purposes of this article, we assume the presence of a normally functioning respiratory system. The blood serves as the vehicle for oxygen delivery. We also assume a normal hemoglobin level (qualitatively and quantitatively). The cardiovascular system serves as the system's pump. Oxygen delivery to the tissues is regulated by the cardiac output (CO) meeting the tissues' requirements.

Dynamic exercise is characterized by a marked increase in the oxygen consumption ($\dot{V}O_2$) with increasing intensity of exercise (Fig 1).[2,3] This increase in $\dot{V}O_2$ is paralleled by a marked increase in the CO and the heart rate (HR).[2,3] Cardiac output begins to increase during the preexercise period,[2] secondary to increased sympathetic activity and increases proportional to the oxygen being consumed. At maximum effort, CO can increase threefold to fourfold above resting levels. The increase in CO is determined by the HR and the stroke volume (SV). Heart rate increases twofold to threefold from the resting state to maximum exercise.[3] When exercise is performed in the upright position, SV will increase from the resting level to one third of maximum effort. Thereafter, little further increase in SV occurs, and further increases of CO are dependent on HR (Fig 1). The SV response is affected by the distensibility of the ventricle (preload), the force of contraction of the ventricle in relation to the pressure in the aorta (afterload). Catecholamines play a role by increasing the force generating potential of the muscle fibers (increasing contractility) increasing the HR and reducing systemic vascular resistance (SVR).[1] When an individual exercises in the supine position, SV is almost at its maximum because of the increased return from the lower body secondary to gravity. Therefore, in the supine position, SV does not increase substantially with ex-

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From the Pediatric Physical Performance Laboratory, Section of Pediatric Cardiology, Department of Pediatrics, Medical College of Georgia, Augusta. Dr Braden is now with the Portsmouth (Va) Naval Hospital.

Reprint requests to Pediatric Cardiology, Medical College of Georgia, Augusta, GA 30912-3710 (Dr Braden).

Table 1.—Types of Exercise

Terminology	Definition
Exercise	Planned, structured, and repetitive body movement done to improve or maintain one or more components of physical fitness
Dynamic (aerobic) exercise*	Exercise involving large muscle groups and producing a predictable and reproducible load on the oxygen transport system by increasing peripheral oxygen demand
Static (isometric) exercise*	Exercise involving smaller muscle groups without a change in the fiber length of the muscles involved; usually submaximal in intensity
Isotonic exercise	Exercise involving the exertion of force that is constant through the full range of motion
Isokinetic exercise	Exercise involving movement of a constant speed

*The terms given in parentheses in each case have similar meanings and can be used interchangeably.

Table 2.—Glossary of Exercise Terms

Terminology	Definition	Commonly Used Measure
Force	The resistance of weight that an individual must move or maintain against gravity	kg
Work	Force times the distance that the force is moved	kgM†
Power	The rate at which work is performed	kgM/min; V_{O_2} (mL/min; L/min)
Maximal effort*	Exercise test that is continued until the $\dot{V}_{O_2}$ no longer increases with an increase in workload	PWC (kgM/min)‡; $\dot{V}_{O_2}$max (mL/min; L/min)
Submaximal effort	Exercise test that is continued to a predetermined level less than maximal	PWC170 (kgM/min)
Ergometry	The process and instrumentation of exercise testing	Cycle (upright, supine), treadmill, arm crank
Intermittent protocol	Graded exercise test involving a resting period between changes in workloads	...
Continuous protocol	Graded exercise test involving no resting period between changes in workloads	...
Maximal voluntary effort (MVE)	Exercise test continued until the subject is no longer willing to continue	PWC (kgM/min)
Aerobic capacity	Marker of fitness determined by the MVE, the time of exercise, the PWC or the $\dot{V}_{O_2}$max	...

*"Maximal effort" is somewhat of a misnomer, because a subject can continue to exercise past a plateau in the amount of oxygen consumed ($\dot{V}_{O_2}$).

†kgM indicates kilogram meter.

‡For uniformity, all data should be indexed by weight (kilograms), height (centimeters), body surface area (square meters), or lean body mass. Therefore, the physical working capacity (PWC) becomes the PWCI, ie, the PWC index, and maximum oxygen consumption ($\dot{V}_{O_2}$max) is indexed and expressed as milliliters per minute per square meter.

ercise. Because of the differences in cardiovascular response associated with position, as well as with the exercise testing protocol being used, it is critical to be knowledgeable about the methods used when comparing results of studies.

Maximum exercise leads to a threefold to fourfold increase in CO. The rise in systolic blood pressure (SBP) and mean arterial pressure (MAP) is linear with the increase in CO. However, if MAP increased fourfold (80 mm Hg to 320 mm Hg), the myocardial demand for oxygen would be so great as to be unsustainable. Dilatation of the systemic arterioles results in a lowering of the SVR. Because of this peripheral vasodilatation, only a minimal change occurs in the diastolic blood pressure (DBP). The MAP is, therefore, much less than it would be if peripheral vasodilatation did not occur.[3] However, because the increase in CO is of a greater magnitude than the increase in MAP, the SVR decreases. Figure 2 demonstrates the interrelationship between the CO, the MAP, the SBP, the DBP, and the SVR with dynamic exercise.

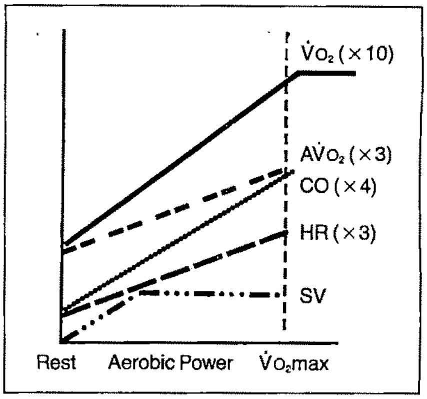

Fig 1.—Cardiovascular responses to upright exercise. CO indicates cardiac output; SV, stroke volume; HR, heart rate; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_2$max, maximum oxygen consumption, and $A\dot{V}O_2$, arteriovenous oxygen difference. The increase in $\dot{V}O_2$ with increasing exercise intensity is paralleled by increases in CO, HR, and $A\dot{V}O_2$.

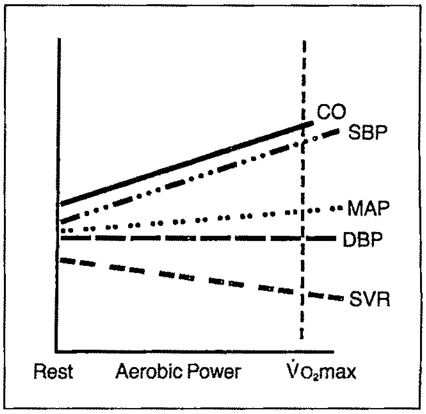

Fig 2.— Blood pressure and systemic vascular resistance (SVR) responses to exercise. CO indicates cardiac output; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; and $\dot{V}O_2$max, maximum oxygen consumption.

Few sports are purely dynamic or isometric. Static or isometric exercise (eg, power lifting) leads to a smaller increase in CO with a greater increase in MAP.[6] In contrast to dynamic exercise (eg, swimming, running, and cycling), the SVR may increase slightly. This occurs because the magnitude of the increase in CO is similar to the magnitude of the increase in MAP. The cardiovascular responses seen with isometric exercise are proportional to the muscle mass involved, the duration of the contraction of the involved muscle groups, and the percentage of maximal tension of the involved muscle group.[7-11]

MEDIATORS OF CARDIOVASCULAR RESPONSES

The normal cardiovascular responses to exercise are affected by several variables, eg, age, sex, ethnicity, exercise protocol (instrument and position), and training.

Age

Children differ from adults in their cardiovascular responses to exercise. Oxygen consumption ($\dot{V}o_2$) can increase up to 10-fold in healthy nontrained children at maximal effort compared with a 10-fold to 15-fold increase in healthy untrained adults. The maximum $\dot{V}o_2$ ($\dot{V}o_2$max) is seen to increase from a value of 1 L/min in a 6-year-old child to 3 L/min in a 15-year-old adolescent,[11] peaking in early adulthood at a level of 3.8 L/min and decreasing thereafter (Fig 3). For comparison, $\dot{V}o_2$max is typically indexed by body weight (in milliliters per minute per kilogram).[12-21]

When indexed by body surface area, the maximum CO (COmax) is somewhat lower in children than in adults and increases with increasing age and increasing stature. Cardiac output is seen to increase by 20 mL/min for each centimeter increase in height for children working at the same $\dot{V}o_2$.[11] On the other hand, children have higher maximal HR (HRmax) values than adults varying from 195 to 215 beats per minute and decreasing after maturity at a rate of 0.7 to 0.8 beats per minute per year (resulting in the commonly used adult formula, HRmax = 220 − age in years), as demonstrated in Fig 4.[2] The maximal SV (SVmax) response to exercise is lower in children than in adults and increases with increasing age and height.[22-24] Increasing age and increasing body size cause an increase in the SBP and the DBP.

Gender

Gender differences have also been observed in the normal cardiovascular responses to exercise with males having greater $\dot{V}o_2$max values than females at almost any age. This has been demonstrated as early as 5 years of age.[21] However, this difference disappears when the $\dot{V}o_2$max is indexed by weight in kilograms or by lean body mass.[20] When the $\dot{V}o_2$max is indexed by weight, it has been observed to increase little in boys and to decrease in girls with increasing age. However, this is a controversial subject, with the literature divided on this topic.[18,20]

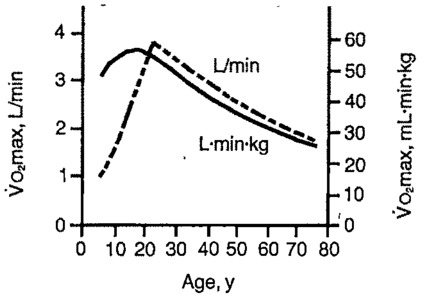

Fig 3.—Effect of age on the maximum oxygen consumption ($\dot{V}o_2$max) in males.

Boys have greater CO responses than girls.[22] However, for a given workload, females have higher HRmax values than do males. This has been considered to be secondary to a smaller lean body mass and lower hemoglobin level in girls at any given weight. However, the same differences in HR are seen in 6-year-old children who have equal hemoglobin concentrations.[25] Other possible explanations include lower SVs in females and sex-related differences in autonomic cardiac regulation. The latter has been postulated because boys have a more rapid decrease in their HR on cessation of exercise than do girls, suggesting a qualitative difference in regulatory mechanisms. Males are also observed to have a greater SV response to maximal exercise than are females at all heights.[22]

Because male adults have a higher SV response than do women to exercise, males have traditionally been thought to have higher SBP responses to exercise than do females. A study[26] of 170 healthy black boys and girls did not support for this assumption. No differences in maximum blood pressure response when indexed by body weight were observed in these children.

Race

The cardiovascular responses to exercise are also affected by race. Recent data from the Medical College of Georgia, Augusta, have shown that black males have SV and CO responses to exercise that are lower in magnitude than those observed in a similar group of white males,[27] suggesting that there may be racial differences in the CO responses to exercise. With similar intensity of exercise, white boys had higher COs.[27]

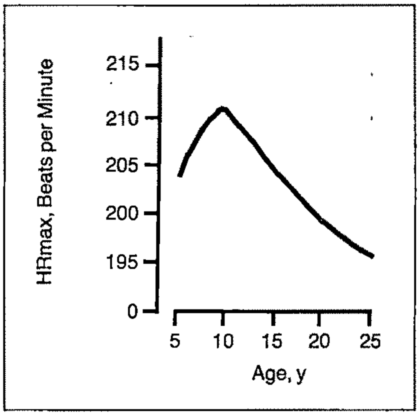

Fig 4.—Effect of age on the maximal heart rate (HRmax) responses to exercise.

Using upright cycle ergometry, no racial differences in HRmax values in children have been demonstrated.[28] Recent studies utilizing supine cycle ergometry demonstrated higher preexercise and HRmax values in white males when compared with age-matched black males.[27]

In a study of 288 healthy children using a treadmill, Riopel et al[29] observed few racial differences with respect to SBP responses to dynamic exercise. However, Alpert et al,[26] using cycle ergometry, demonstrated that black males had higher exercise blood pressure responses than white males indexed by age and by body surface area (Fig 5). However, these black youths also tended to have a greater aerobic power than their white counterparts.

Recently, Arensman et al[27] demonstrated that black males exhibit a more marked increase in SVR with maximal exercise than a white male cohort. This accentuated SVR response is associated with the previously mentioned diminished CO response to maximal exercise.

Exercise Protocol

The type of ergometer and the exercise position also affect the normal child's cardiovascular responses to exercise. Standards exist for cycle and

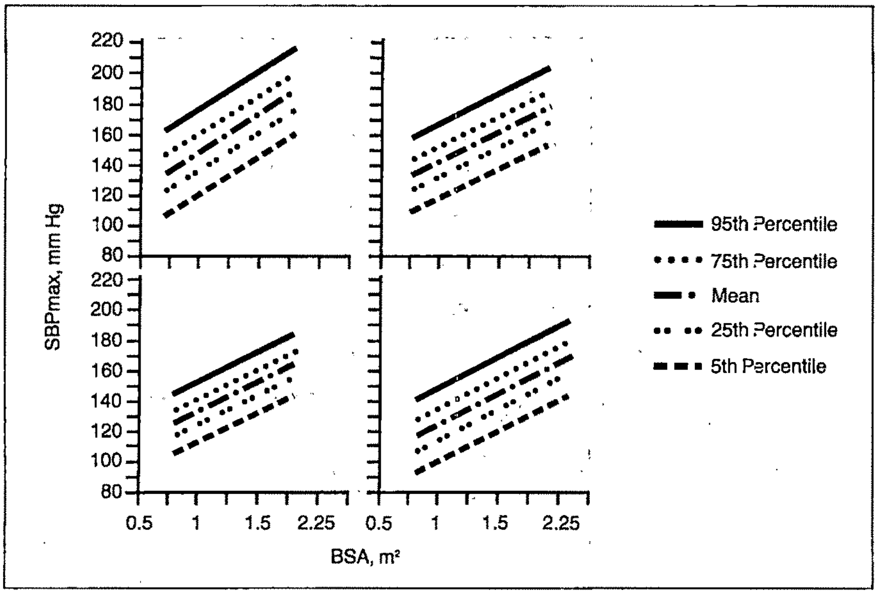

Fig 5.—Effect of race on maximal blood pressure responses to exercise in black females (top left), black males (top right), white females (bottom left), and white males (bottom right). SBPmax indicates maximum systolic blood pressure; BSA, body surface area.

treadmill exercise protocols. The methods used are often determined by ergometer availability, variables to be assessed, and physician preference. Treadmill exercise produces a higher myocardial $\dot{V}O_2$ and, therefore, a higher total $\dot{V}O_2$. However, upright cycle ergometry is generally safer and quieter, and allows easier measurement of multiple variables. Supine cycling, although not as commonly used, is particularly amenable to Doppler assessment of CO.[27] Doppler-derived COs can be coupled with $\dot{V}O_2$ and workloads to give a more complete assessment of working capacity and cardiovascular response to exercise.

Higher $\dot{V}O_2$max values, CO, and HRmax are observed in treadmill exercise when compared with cycle ergometry due to the individual being unsupported and using a greater muscle mass in treadmill exercise.[14,29,30] Treadmill exercise causes greater SV and blood pressure responses in adults, but there are insufficient data on the effects of these variables in children.

Table 3.—Effect of Different Variables on Cardiovascular Responses to Exercise

Cardiovascular Response*	Age†	Children vs Adults	Gender	Race	Instrument	Position
$\dot{V}O_2$max	↑s to early 20s	Lower	M>F; M=F when indexed/kg	Insufficient data	Treadmill > cycle	Upright > supine
COmax	↑s	Lower	M>F	W≥B	Treadmill > cycle	Upright > supine
HRmax	↓s after	Higher	M=F (F>M, submaximal HR)	W≥B	Treadmill > cycle	Upright > supine
SVmax	↑s	Lower	M>F	W≥B	Treadmill > cycle‡	Supine > upright
BP	↑s	Lower	M=F	B≥W	Treadmill > cycle‡	Insufficient data

*$\dot{V}O_2$max indicates maximum oxygen consumption; COmax, maximum cardiac output; HRmax, maximal heart rate; SVmax, maximum stroke volume; and BP, blood pressure.

†Upward arrows indicate increases; downward arrows, decreases.

‡Adult data.

Table 4.—Responses of Maximum Oxygen Consumption ($\dot{V}O_2$max) to Training

Variable	Brown et al[36]	Ekblom[37]	Lussier and Buskirk[38]	Eriksson and Koch[24]	Vaccaro and Clarke[35]	Massicotte and MacNab[39]	Rotstein et al[40]
No. of subjects	12	6	16	9	15	9	28
Sex	F	M	M, F	M	M, F	M	M
Age, y	8-13	11	8-12	11-13	9-11	11-13	10-12
Weeks of study	6, 12	24	12	16	28	6	9
Time session	...	45	45	60	...	12	45
Days per week	4-5	...	4	3	4	3	3
% increase in $\dot{V}O_2$max	18, 26	10	7	16	10	11	8

Upright cycle exercise produces a higher $\dot{V}O_2$max value and more marked changes in CO than does supine cycle exercise. This is a result of greater values for HRmax and SVmax.[23,24] Supine exercise causes a greater increase in venous return from exercising of the lower extremities, leading to a greater SV at rest and secondarily lower values for resting HR and HRmax. Because of the greater increase in SV in the preexercise state, the early increase in SV is not usually observed during supine exercise.

Table 3 summarizes the effect of age, gender, race, and protocol on the cardiovascular responses to dynamic exercise.

Response to Training

Athletic training in adults causes an increase in total blood volume and total hemoglobin level, leading to an increase in the venous return to the heart and a secondary increase in SV.[31] However, these hematologic changes are not accompanied by an increase in the absolute hemoglobin concentration. Trained pubertal children exhibit similar responses to those seen in adults, with an increase in SV at all levels of exercise. However, these increases have not been consistently demonstrated in prepubertal children. The changes in adolescents and adults are thought to be secondary to higher SV and improved venous return and/or improved myocardial contractility.

Trained athletes also demonstrate lower resting HRs, lower HRs at all exercise levels, and a more rapid decline in HR after exercise (recovery). The resting HR and submaximal HRs are considered to be the most sensitive reflectors of conditioning and often precede any changes in maximal aerobic power. The sensitivity of this HR response forms the basis for use in fitness tests in which the $\dot{V}O_2$max is indirectly assessed from the submaximal HR. The HR changes are opposed by changes in the SV in the opposite direction, thus leading to little change in the CO at any given metabolic level. However, the maximal CO in children is seen to increase in training in proportion to the increase in the $\dot{V}O_2$max observed in childhood athletes.[32-35] Table 4 demonstrates that prepubertal children may also be responsive to cardiovascular training. This table, compiled by Snell, illustrates the increase in $\dot{V}O_2$max occurring in children secondary to training as observed by several authors.[36-40]

Echocardiographic studies have demonstrated training-induced changes in postpubescent athletes.[41-43] These observed findings reflect the effect of increased heart volume work secondary to training with echocardiographic evidence of left ventricular dilatation. There may also be increased left ventricular muscle secondary to increased chamber size and myocardial hypertrophy. Prepubescent athletes may also exhibit echocardiographic evidence of increased left ventricular volume and myocardial hypertrophy.[44]

Figure 6 demonstrates the relationship among HR, $\dot{V}O_2$max, serum lactate concentration, minute ventilation, and the carbon dioxide production. The *ventilatory threshold* (VT) (or anaerobic threshold) is the "point" during a progressively graded exercise test when minute ventilation and carbon dioxide production curves separate from the linear rise in the $\dot{V}O_2$. The *anaerobic threshold* is the point at which lactate begins to accumulate in the blood. It is now believed that the anaerobic threshold or VT is merely a manifestation of lactate accumulation secondary to an inability of the kidney to clear the lactate as rapidly as it is produced. This increase in lactate concentration causes a marked increase in both the minute ventilation and the carbon dioxide production. The increase in lactate concentration and the VT do not necessarily occur at the same point, and it is, therefore, difficult to identify consistently a point at which the VT occurs. Regardless, many exercise physiologists consider the VT to be a good measure of one's exercise "efficiency" and believe it to be a better measure of aerobic fitness than the $\dot{V}O_2$max. The VT is often expressed as a percentage of the $\dot{V}O_2$max, or of the exercise time, or of the HRmax. Wolfe et al[45] studied the VT in 10 prepubertal female cross-country runners as a possible predictor of athletic performance. The $\dot{V}O_2$max in that study was seen to predict performance rank at a statistically significant level. The VT expressed as a percentage of the $\dot{V}O_2$max also predicted performance, but at a less significant level. The best predictor of performance was the VT, expressed as either a percentage of the exercise time or of the HRmax.

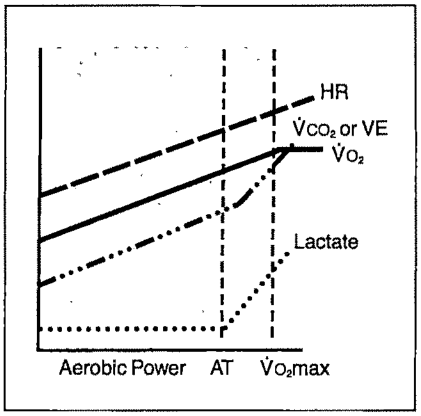

Fig 6.—The relationship between heart rate (HR), maximum oxygen consumption ($\dot{V}O_2$max), and the anaerobic threshold (AT). VE indicates minute ventilation; $\dot{V}O_2$, oxygen consumption; and $\dot{V}CO_2$, carbon dioxide production.

As has been demonstrated, pediatric cardiovascular responses to exercise are similar to those of adults in quality, with the quantitative aspects dependent on the size, age, and dimensions of the child. Many of these variables are also affected by the sex and race of the child. These cardiovascular responses are also affected by the physician, the methods involved, and the training of the child.

CONCLUSION

Oxygen consumption increases with increasing exercise intensity. This increase in $\dot{V}O_2$ is paralleled by an increase in the CO and the HR. The increase in $\dot{V}O_2$ is also paralleled by an increase in SV, with the maximum increase occurring at one third of the maximal exercise intensity. The increased CO is associated with an increase in SBP, but SVR decreases with maximal dynamic exercise secondary to systemic vasodilatation. Maximum oxygen consumption and the VT may serve as indicators of aerobic power in children.

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Table 4 was compiled by Peter Snell, PhD, University of Texas Medical Center, Galveston, for use in Grand Rounds presentations.

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Articles

β-Galactosidase Tablets in the Treatment of Lactose Intolerance in Pediatrics

Marvin S. Medow, PhD; Kerry D. Thek, MD; Leonard J. Newman, MD; Stuart Berezin, MD;
Mark S. Glassman, MD; Steven M. Schwarz, MD

• Lactose-intolerant children manifest diminished or nonexistent intestinal lactase activity, resulting in flatulence, abdominal pain, and diarrhea. To assess the hydrolytic capability of lactase-containing tablets taken immediately before oral lactose challenge, we studied 18 children previously identified as being lactose intolerant and having no underlying organic gastrointestinal disease. Subjects had a mean (±SEM) age of 11.4±3.4 years; 72% were male. At time of the study, lactase-containing tablets or placebo tablets were ingested (double-blind) immediately before drinking a solution of lactose. Breath samples were obtained for hydrogen analysis at 30-minute intervals during a 2-hour period, and clinical symptoms were monitored. In lactose-intolerant patients, hydrogen production was significantly greater following placebo (maximum hydrogen excretion, approximately 60 ppm) compared with lactase-containing tablets (maximum hydrogen excretion, 7 ppm). Increased hydrogen production was associated with clinical symptoms including abdominal pain (89% of subjects following placebo ingestion), bloating (83%), diarrhea (61%), and flatulence (44%). These results indicate, therefore, that coingestion of lactose and lactase-containing tablets significantly reduces both breath hydrogen excretion and clinical symptoms associated with lactose intolerance.

(*AJDC.* 1990;144:1261-1264).

Lactose intolerance, a consequence of decreased or absent intestinal β-galactosidase (lactase) activity, is a common finding in the pediatric population.[1,2] Symptoms related to lactose intolerance are often transient, presenting as a result of mucosal injury associated with either bacterial or viral enteritis.[3,4] Other clinical states characterized by intestinal brush-border injury or altered bowel flora (eg, gluten-sensitive enteropathy and gastrointestinal surgery) may be complicated by secondary lactase deficiency.[5,6] A rare, congenital form of this disorder characteristically presents within the first few days of life, following introduction of lactose in breast milk or formula.[7,8] In otherwise healthy older children and adults, the inability to hydrolyze lactose to its component sugars, glucose and galactose, is commonly referred to as "late-onset" or "acquired" lactase deficiency. This type of enzyme disorder is thought to occur as a heritable, autosomal recessive trait, exhibiting a wide variation in incidence among different ethnic groups. Symptoms, while usually noted after 3 to 5 years of age, may occur as late as adolescence.[1,2]

The clinical consequences of lactase deficiency result from the bacterial hydrolysis of lactose in the cecum and colon, resulting in production of hydrogen, carbon dioxide, and short-chain organic acids.[9-11] Increased evolution of gas, and the osmotic load presented to the colon secondary to bacterial fermentation can lead to multiple symptoms, including abdominal pain, distention, flatus, eructation, and watery, often acidic stools. In children with lactase deficiency, these symptoms may result in anorexia and weight loss.

Because milk and dairy products are important sources of both macronutrients and micronutrients in the pediatric diet, a convenient treatment for lactose intolerance may obviate the need for specialized nutritional management. Current available therapies include commercially available predigested milk and dairy products as well as fungal or yeast-derived β-galactosidases added to lactose-containing liquids. While this latter treatment is effective, 12 to 24 hours is required for adequate (ie, >60%) in vitro lactose hydrolysis. Recent studies have described the utility of adding β-galactosidases to milk immediately before ingestion by adults[12,13] and children[14,15] in decreasing both the production of breath hydrogen and the clinical symptoms associated with lactose intolerance. To determine an effective treatment alternative for children with

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From the Department of Pediatrics, Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Valhalla.

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Reprint requests to the Department of Pediatrics, Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Valhalla, NY 10595 (Dr Medow).

symptomatic lactose intolerance, we evaluated the efficacy of a tablet form of β-galactosidase taken immediately before an oral lactose challenge.

PATIENTS AND METHODS

Patient Selection

Patients were selected from among those referred to the Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Valhalla. Patients presenting with chronic nonspecific abdominal pain, with or without diarrhea, were evaluated for the presence of late-onset primary lactose intolerance.

Children with underlying gastrointestinal disease (eg, inflammatory bowel disease, acute gastroenteritis, and celiac disease) or manifestations of acute/chronic malnutrition or growth failure[16] were excluded from the study. Routine patient screening included a physical examination; determinations of complete blood cell count with differential cell count, platelet count, erythrocyte sedimentation rate, and liver function; and urinalysis and urine culture. Those with normal results of screening studies subsequently underwent breath hydrogen analysis, as described below.

From December 1, 1987, through November 30, 1988, a total of 18 patients with late-onset lactose intolerance were enrolled in the study. The protocol was approved by The Committee for the Protection of Human Subjects (Institutional Review Board), New York Medical College.

Hydrogen Breath Testing

All patients fasted for a minimum of 8 hours before the hydrogen breath test was performed and had not received antibiotics for at least 2 weeks before the test. Participants were placed on a gluten- and lactose-free diet for 24 hours before testing to minimize basal hydrogen production. Each patient received lactose (2 g/kg of body weight up to a maximum of 50 g) and had serial breath samples (0, 30, 60, 90, and 120 minutes following lactose ingestion) tested for the presence of hydrogen. Patients who did not produce hydrogen after a carbohydrate challenge, or those who exhibited baseline (zero time) breath hydrogen levels greater than 10 ppm, were excluded from the study.

Lactose-intolerant patients who agreed to participate underwent two additional breath tests at least 2 weeks apart, during which either lactase-containing tablets or placebo tablets were administered in a double-blind, cross-over fashion. The investigator initially determined which tablet to administer in a randomized fashion by lot. Tablets containing lactase (β-galactosidase produced from *Aspergillus oryzae*) and placebo of inert excipient were supplied by Lactaid Inc, Pleasantville, NJ. Each active tablet contained 3000 (Food Chemical Codex Units) of β-galactosidase (optimum pH, approximately 4.5). Participants chewed and swallowed one tablet per 5 g of lactose immediately before carbohydrate challenge. There were no sensory differences (ie, taste or texture) between the active and placebo tablets.

End expiratory breath samples were collected in a gas-tight syringe and analyzed for hydrogen concentration following separation with use of a gas chromatograph (Carle Model AGC 111, Hache Inc, Loveland, Colo) with a 275-cm, 5 Å molecular sieve column (45/50 mesh) equipped with a thermal conductivity detector. The system was standardized before each use with a reference gas consisting of 100 ppm of hydrogen in nitrogen (MG Scientific Gases, Northbranch, NJ). Hydrogen concentration was quantitated with use of a computing integrator (Shimadzu CR3A, Shimadzu Inc, Columbia, Md). Breath hydrogen levels 10 ppm above baseline were considered positive for lactose malabsorption.[15]

Symptom Evaluation

During each of the carbohydrate challenges, patients were interviewed about the presence or absence of abdominal pain, gas, bloating, diarrhea, or flatulence. In addition, patients recorded their symptoms on a questionnaire, which was evaluated for severity of symptoms (on a scale of 1 to 5, with 1 being absence of symptoms and 5 being severe symptoms) independent of breath analysis results.

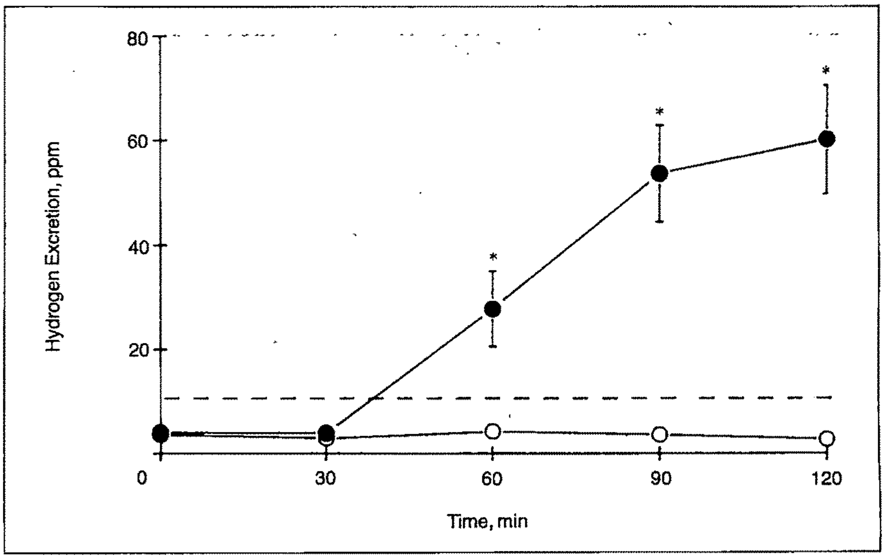
Statistical Analysis

Comparisons between lactose-tolerant and lactose-intolerant patients were made with use of both χ^2 analysis and Student's t test for unpaired samples (two-tailed). Differences in hydrogen excretion associated with placebo and lactase treatment were assessed with use of Student's t test for paired data (two-tailed).[17]

RESULTS

During the examination of 160 children (mean ± SEM age, 9.3 ± 0.4 years) referred because of chronic recurrent abdominal pain, 55 (34%) were identified as being lactose intolerant. Patients were classified as being either lactose-tolerant (normal) or lactose-intolerant based on the results of breath hydrogen analysis every 30 minutes for a total of 120 minutes. In lactose-tolerant children (Fig 1), breath hydrogen excretion did not exceed 10 ppm, as shown by the broken line in Fig 1, and averaged (mean ± SEM) 2.3 + 0.2 ppm up to 120 minutes. Breath hydrogen quantitation of lactose-intolerant children exceeded 10 ppm by 60 minutes and remained significantly elevated ($P<.01$, normal

Fig 1.—Time course of breath hydrogen excretion in lactose-tolerant (open circles) and lactose-intolerant (closed circles) patients (N = 160). Data shown are the mean (± SEM) breath hydrogen excretion values; where not depicted, SEM is within the data point. The dashed line represents a breath hydrogen level of 10 ppm; breath hydrogen concentration above 10 ppm is diagnostic of lactose malabsorption. Asterisk indicates $P<.01$, normal vs control.



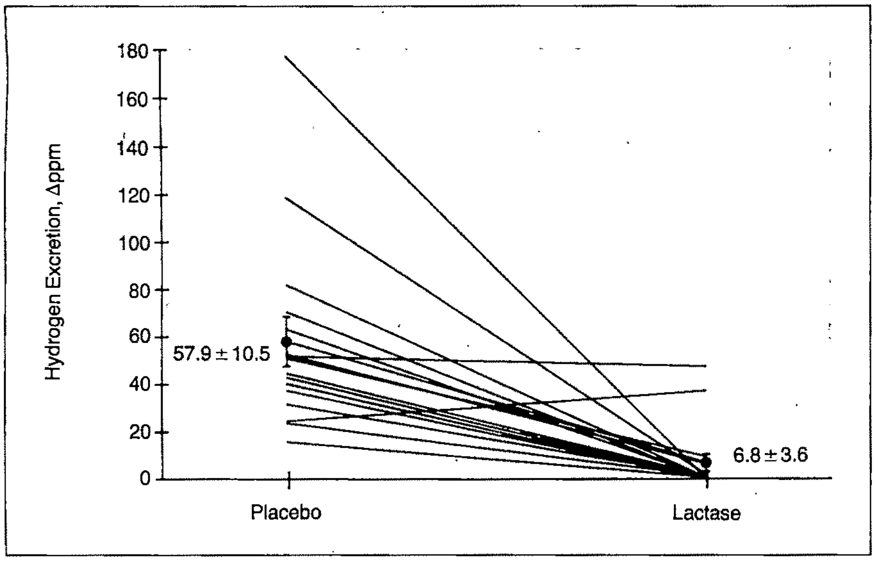


Fig 2.—Breath hydrogen excretion of 18 patients determined 120 minutes after lactose ingestion with either placebo- or lactase-containing tablets. Data shown are individual values of net (total minus basal) breath hydrogen excretion. Solid circles indicate the mean (± SEM) values ($P<.01$, placebo vs lactase tablets).

Symptoms Recorded by 18 Study Patients*

Symptom	No. of Patients Lactase Group	Placebo Group
Diarrhea	1	11
Bloating	. . .	15
Abdominal pain	1	16
Flatulence	. . .	8
Total	**2**	**50**

*Symptoms were recorded following lactose challenge (2 g/kg; maximum dose, 50 g) plus either placebo or lactase tablets (1 tablet per 5 g of lactose) (see "Patients and Methods" section).

vs lactose-intolerant; N = 160) for the duration of the test period. There were no differences at zero time (3.7 ± 0.44 vs 4.1 ± 1.43 ppm) or at 30 minutes (2.9 ± 0.36 vs 3.9 ± 1.28 ppm) (mean ± SEM), comparing breath hydrogen levels for all normal and lactose-intolerant patients, respectively.

Eighteen of the 55 patients identified as lactose intolerant agreed to participate in this study. The demographics of the participants were not different from those of the nonparticipants. The mean age of the participants was 11.4 ± 3.4 years, which was not significantly different from that of the 160 children initially screened for lactose intolerance. The sex distribution was 72% male compared with 47.5% of the initial group. Figure 2 shows that placebo administration, followed by lactose challenge, resulted in a mean (± SEM) net breath hydrogen value of 57.9 ± 10.5 ppm at 120 minutes (net hydrogen excretion equals total minus basal [zero time] levels). In contrast, lactose-intolerant patients produced only 6.8 ± 3.6 ppm of hydrogen at 120 minutes ($P<.01$, $n = 18$). Figure 2 also shows maximum net breath hydrogen values for each patient following both placebo and lactase administration. In 16 (89%) of the 18 participants, lactase pretreatment successfully lowered maximal (120-minute) net breath hydrogen levels to below the 10-ppm threshold for malabsorption ($P<.001$).

The Table lists the clinical symptoms associated with lactose challenge in this pediatric population. Following placebo, 89% of patients experienced abdominal pain, 83% experienced bloating, 61% experienced diarrhea, and 44% experienced flatulence. In two (11%) of the 18 patients, symptoms were reported despite pretreatment with lactase calculated to hydrolyze the ingested lactose load.

COMMENT

Lactose malabsorption resulting from lactase deficiency can be detected by a lack of rise in plasma glucose level following ingestion of lactose. A less invasive, more accurate method for the detection of lactase deficiency is the measurement of breath hydrogen. Because hydrogen is not produced as a result of normal metabolism in humans, bacterial fermentation of nonhydrolyzed lactose produces hydrogen that diffuses into the blood and can be measured in expired breath. The presence of increasing amounts of breath hydrogen with time following an oral lactose load suggests lactase deficiency. In some 20% of patients studied, however, colonic bacteria were incapable of producing hydrogen when presented with a nonmetabolizable carbohydrate, lactulose.[18] In these individuals, determination of breath hydrogen excretion is of little diagnostic value. Our study, therefore, included patients who were symptomatic and capable of producing hydrogen gas.

Numerous clinical studies have described the efficacy of the predigestion of lactose in the elimination of symptoms associated with lactase deficiency.[12-15] These investigations included the predigestion of milk or lactose-containing formula before ingestion. However, there has been no correlation of symptoms with breath hydrogen production in older children and adolescents, nor an evaluation of the effectiveness of lactase and lactose co-administration. We evaluated the effectiveness of lactase-containing tablets in the reduction of breath hydrogen excretion and clinical symptoms commonly associated with lactase deficiency. The participants were healthy, well-nourished children diagnosed as being lactose intolerant. Breath hydrogen was measured every 30 minutes for 2 hours following lactose ingestion, rather than for 3 or 6 hours as suggested by some investigators,[19,20] as breath hydrogen excretion was significantly greater than the basal level by 60 minutes. Our results show that coingestion of lactose and lactase-containing tablets significantly reduced breath hydrogen excretion in 16 (89%) or 18 patients. This reduction in hydrogen excretion was temporally associated with a decrease of reported symptoms in this group of lactose-intolerant patients. Use of a convenient, palatable tablet form of lactase offers obvious advantages, allowing for the potential liberalization of dietary lactose intake. The inability of lactase tablets to lower breath hydrogen excretion and ameliorate symptoms in two patients may have been secondary to several factors. For example, gastric hyperacidity may have resulted in decreased activity of the enzyme (optimum pH, approximately 4.5). Alternatively, selected patients may be exquisitely sensitive to small amounts of unhydrolyzed carbohydrate, requiring increased exogenous lactase.

Lactose intolerance in this study was evaluated using a standard carbohydrate challenge, which employs a nonbuffered solution of lactose in water (pH 6.2). It is likely that the pH of this solution in the stomach approximated the optimum of the exogenous lactase and resulted in relatively rapid hydrolysis of the ingested lactose. Caution must be exercised, however, when extrapolating from results obtained with use of a lactose solution to results achieved with ingestion of lactose-containing foods. Hydrolysis of a lactose solution is not limited by factors such as degree of mastication, mechanical disruption, enzymatic predigestion of complex carbohydrates, and effective exposure of lactose to the exogenous enzyme. Furthermore, the buffering effect of dietary proteins and the variability in gastric emptying time as a consequence of dietary composition may influence the effectiveness of exogenous lactase. Further studies with various lactose-containing foods are therefore required to establish the utility of oral lactase administration in the reduction of both breath hydrogen excretion and related gastrointestinal symptoms associated with lactose intolerance in children.

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Risk Factors for Adolescent Cigarette Smoking

The Muscatine Study

Thomas M. Reimers, PhD; Paul R. Pomrehn, MD; Samuel L. Becker, PhD; Ronald M. Lauer, MD

• Smoking among adolescents is a developmental phenomenon with several factors exerting an influence on cigarette use at different times. We examined the longitudinal influences of several behavioral and social variables on the smoking status of 443 students followed from early to late adolescence. Of the factors examined, association with friends who smoke and previous smoking status were consistently associated with an adolescent's future smoking status. Other factors, such as attachment to father or to mother, parental supervision, extracurricular activity, perceived negative and positive effects of smoking, and academic involvement, were all related to late adolescent smoking status. These observations suggest that strategies that influence smoking behavior need to be directed not only to the individual child but also to influences within the child's home and school environment.

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Cigarette smoking is a major preventable cause of death.[1] It has been estimated that 20% of high school senior girls and 16% of boys smoke daily.[2] The negative health consequences of smoking, the implications for prevention, and the emergence of the smoking habit during adolescence have resulted in a large number of investigations focusing on adolescent cigarette use.[3,4]

Research on adolescent smoking has identified a number of risk factors. The most consistent influence on adolescent cigarette use is the association with friends who smoke.[3-7] Studies have demonstrated that adolescents who smoke tend to associate with other adolescents who smoke. Several other factors also are related to adolescent cigarette use, including adolescents' relationship with or attachment to their parents,[8,9] level of parental supervision,[10] involvement in extracurricular activities,[3,8,11] school performance,[4,5,12] and attitudes regarding the negative and positive consequences of smoking.[4,13]

Most research in this area has treated smoking as a static event, ie, many of the investigations have been cross-sectional, examining influences on smoking behavior at a specific time. The primary purpose of this investigation was to identify factors that exert the greatest influence on future smoking behavior and to ascertain whether the influence of these factors changes over time.

SUBJECTS AND METHODS

Population

Students attending two junior high schools and one high school in Muscatine, Iowa, were administered standardized questionnaires during each spring from 1981 through 1984. The group response to questions related to smoking behavior previously had been validated against salivary thiocyanate measurements.[14,15] All students attending grades 8 through 11 were surveyed in their homerooms by a trained research staff. The students ranged in age from 13 to 17 years. The current analyses were based on 443 students who were present at each of the four yearly survey administrations. Those who were absent from one or more surveys were excluded. This resulted in a loss of 262 students from a total pool of 705 students. To determine whether the subjects being analyzed were representative of the total pool, they were compared with the 262 subjects who were excluded. Comparisons were made for age, sex, eight prediction variables, and the dependent variable of smoking status in the 11th grade. No significant difference was found in any of these comparisons.

Predictor Variables Used in the Analyses

Forty-nine items were selected from a multi-item questionnaire to form nine composite variables that previous research had shown to be related to smoking.[4,9] Cronbach's α coefficient was computed to assess the interitem reliability of seven of the nine composite variables. Cronbach's α coefficient ranges from 0 to 1.0, with a score of 1.0 indicating perfect reliability. The composite variables were as follows.

Association With Friends Who Smoke.—This scale was based on a total of six items that measured how many of the subject's friends smoked. Three items were directed toward friends of both sexes: friends known the longest, friends with whom they associated most often, and best friends. The smoking behavior of these friends was assessed on a four-point Likert scale, ranging from 1 (none smoke) to 4 (all or almost all smoke). Cronbach's α coefficient for this scale was 0.90, indicating that the interitem reliability for this variable was high. A high score on this variable indicated a more frequent association with friends who smoke.

Attachment to Father.—This scale consisted of four items that measured the degree to which a subject's father seemed to understand the subject, praised or complimented the subject, made the subject feel close to him, and talked over problems with the subject. These paternal characteristics were scored on a scale ranging from 1 (never) to 4 (usually). Cronbach's α coefficient for this scale was 0.91.

Attachment to Mother.—This scale applied the same four characteristics as the attachment to father scale. Cronbach's α coefficient for this scale was 0.90.

Parental Supervision.—This two-item scale measured the degree to which the mother and father knew where the subject was when he or she was away from home.

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From the Departments of Pediatrics (Drs Reimers and Lauer), Preventive Medicine and Environmental Health (Drs Pomrehn and Lauer), and Communication Studies (Dr Becker), The University of Iowa, Iowa City. Dr Reimers is now with the Children's Memorial Hospital and Creighton University School of Medicine, Omaha, Neb.

Reprint requests to The Muscatine Study, Division of Pediatric Cardiology, W139 GH, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Responses on these items ranged from 1 (never) to 4 (usually). Cronbach's α coefficient for this scale was 0.72.

Extracurricular Activity.—This two-item scale assessed the level of importance of athletics and other school-related activities to the subject. Each item was rated on a four-point Likert scale ranging from 1 (not important at all) to 4 (very important). Cronbach's α coefficient for this scale was 0.74.

Negative Effects of Smoking.—This 12-item composite assessed subjects' perception of the negative effects that accompany smoking concerning the extent to which smoking produces coughing, harms health, shortens breath, costs too much money, hurts sports ability and schoolwork, smells bad, makes you sick, makes you feel bad, is a bad habit, upsets your stomach, or tastes bad. Subjects were asked to endorse each of these effects that they thought would happen to them from smoking. The items endorsed by each subject were summed to form the composite score. A high score on this scale indicated a greater association of negative effects with cigarette smoking. Because each item was simply endorsed or not endorsed, Cronbach's α coefficient was not computed.

Positive Effects of Smoking.—This 13-item composite measured perceptions of the positive effects that accompany smoking concerning the extent to which smoking is rewarding, calms you, feels good, is satisfying, makes you look sophisticated and grown-up, makes you feel more sociable, helps to control weight, makes you relax, is enjoyable, makes you feel like an adult, stimulates you, helps you get along better with others, or helps you to think. Subjects were asked to endorse each of these positive effects that they thought smoking would have on them. The number of items endorsed by a subject formed the composite score. Thus, a high score on this composite indicated a greater association of positive effects with cigarette smoking.

Academic Involvement.—This three-item scale assessed the general school and learning environment of each subject. The scale was composed of students' grade point averages, the amount of time spent doing homework, and a measure of how rewarding schoolwork and grades were to them. Cronbach's α coefficient for this scale was 0.56.

Parental Smoking.—This two-item scale measured how much each subject's mother and father smoked. Responses to each item ranged from 1 (never smoked) to 5 (nearly every day or every day). Cronbach's α coefficient for this scale was 0.61.

Nonresponse Indicator Variables

To assess the influence of data that were missing due to failure or refusal to respond to an item, "indicator" variables were developed for each of the nine predictor variables.[16] For these variables, responses were scored 0, and nonresponses were scored 1. These indicator variables allowed us to determine if failure to answer a question was a significant predictor of future smoking status. We hypothesized that failure to answer an item would be associated with a subject's attitudes, beliefs, or behaviors concerning smoking. Thus, a significant indicator variable would suggest that data were not missing at random, but missing responses were associated with smoking status.

Table 1.—Percentage and Number of Cases Categorized as Nonsmokers, Experimenters, and Regular Smokers, by Grade and Sex*

	% (No.)		
Grade, Sex	**Nonsmoker**	**Experimenter**	**Regular Smoker**
8th			
Total	86.9 **(385)**	7.2 **(32)**	2.7 **(12)**
M	86.9 (185)	7.0 (15)	3.3 (7)
F	87.0 (200)	7.4 (17)	2.2 (5)
9th			
Total	83.1 **(368)**	9.5 **(42)**	4.3 **(19)**
M	81.2 (173)	10.8 (23)	4.7 (10)
F	84.8 (195)	8.3 (19)	3.9 (9)
10th			
Total	80.8 **(358)**	7.0 **(31)**	9.3 **(41)**
M	80.8 (172)	5.6 (12)	10.8 (23)
F	80.9 (186)	8.3 (19)	7.8 (18)
11th			
Total	68.4 **(303)**	12.4 **(55)**	14.7 **(65)**
M	63.8 (136)	13.6 (29)	16.9 (36)
F	72.6 (167)	11.3 (26)	12.6 (29)

*Percentages do not add to 100% owing to a small percentage of subjects who did not "fit" the definition of nonsmoker, experimenter, or regular smoker across grades.

Measure of Smoking Status

This scale, constituting the dependent variable, was composed of two items. The first item asked how much the student used cigarettes with the following possible responses: (1) never used, (2) smoked once or twice, (3) smoked a few times, (4) smoked occasionally but less than once a month, (5) smoked weekly but not every day, and (6) smoked every day or nearly every day. The second item asked how many cigarettes the respondent smoked per day with the following possible responses: (1) do not smoke at all, (2) smoke but not every day, (3) smoke daily but fewer than 5 cigarettes per day, (4) smoke 5 to 10 cigarettes per day, (5) smoke 11 to 20 cigarettes per day, and (6) smoke 20 or more cigarettes a day. Responses from the two items were combined to form three categories of smoking status.

Nonsmoker.—Subjects in this category reported on the first item that they had never smoked, had smoked once or twice, or had smoked a few times, and reported on the second item that they did not smoke at all. Thus, this category included adolescents who had never smoked a cigarette as well as those who had tried smoking but were not smoking when the survey was taken.

Experimenter.—This category consisted of those adolescents who indicated on the first item that they had smoked once or twice, had smoked a few times, or smoked occasionally but less than once a month, and reported on the second item that they smoked but not every day.

Regular Smoker.—Adolescents categorized as regular smokers reported on the first item that they smoked weekly (but not every day), or that they smoked every day or nearly every day, and responded on the second item that they smoked daily but less than 5 cigarettes per day, smoked 11 to 20 cigarettes per day, or smoked 20 or more cigarettes per day.

Statistical Methods

Discriminant analysis[17] was used to identify the variables that best discriminated between the 11th grade (oldest examined age in this study) nonsmokers, experimenters, and regular smokers at different times. The predictor variables were used in separate analyses to identify which variables from each survey point (8th, 9th, 10th, and 11th grades) best discriminated among the 11th grade nonsmokers, experimenters, and regular smokers. This procedure made possible an assessment of the degree to which the smoking of 11th graders could be predicted with measures obtained at the 8th grade alone, the 9th grade alone, the 10th grade alone, and the 11th grade alone.

This analysis allows for an examination of the relative contribution of each variable within a particular analysis.[18] The computed values that measure the relative contribution of each variable are referred to as standardized canonical discriminant coefficients (standardized coefficients). The larger the magnitude of a standardized coefficient, the greater the relative contribution of that variable to the prediction. The discriminant analyses generated two functions, with each function having its own set of standardized coefficients. Only the standardized coefficients from the first function were reported because of the small contribution to the overall discrimination made by the second function.

We used this procedure to test how well we were able to classify or to predict smoking status at the 11th grade (ie, whether each subject was a nonsmoker, an experimenter, or a regular smoker) based on the significant variables included in each analysis. The discriminant analysis provided a comparison of the known actual group (based on their self-report) of nonsmokers, experimenters, and regular smokers with those predicted to be included in one of these groups based on responses to the predictor variables.

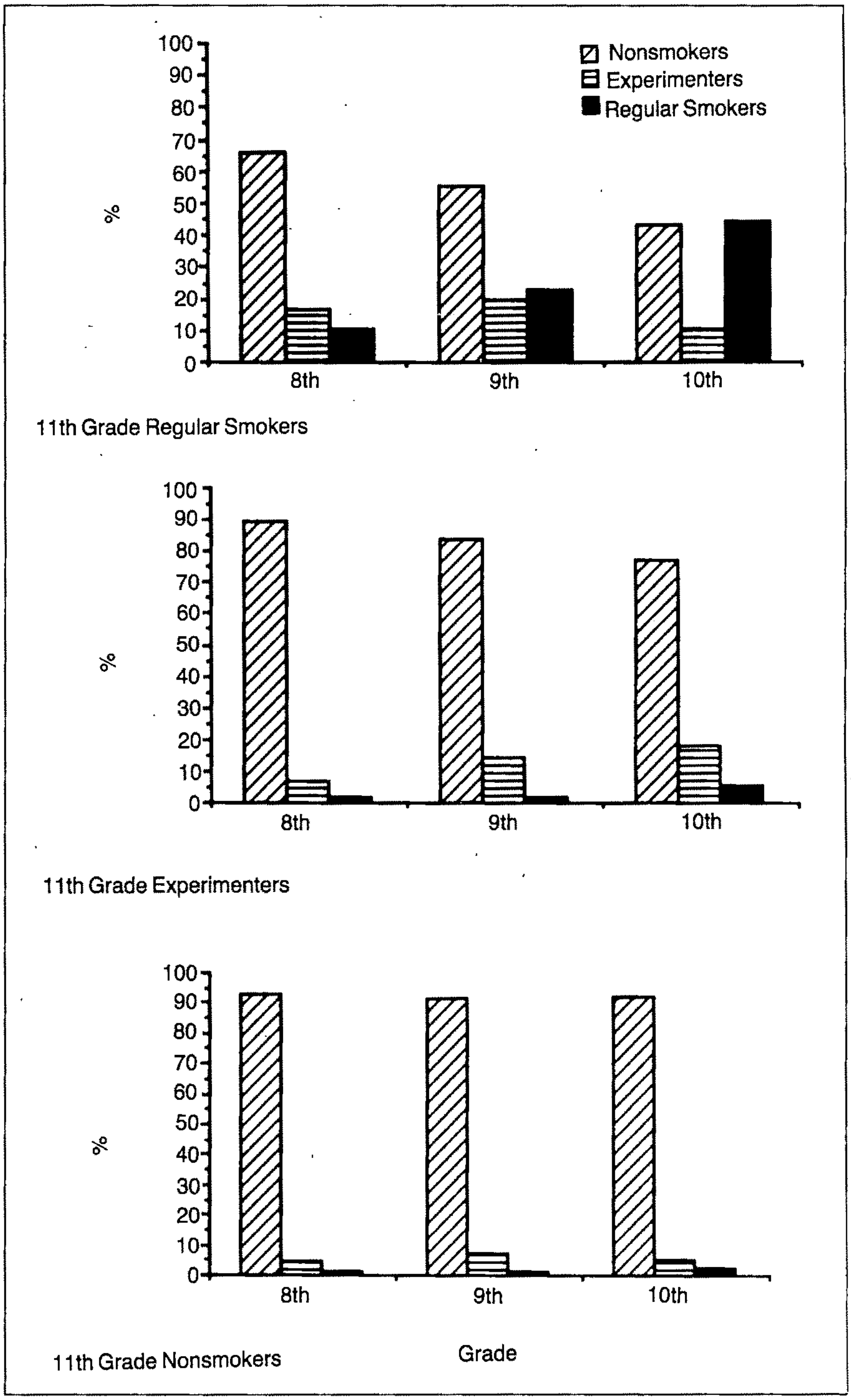
A multivariate analysis of variance (MANOVA) was conducted for each composite variable to determine whether responses to these variables by nonsmokers and regular smokers changed in different ways as they progressed from grade to grade (ie, 8th to 9th, 9th to 10th, and 10th to 11th)—ie, in statistical terms, whether an interaction between smoking status and grade level on that variable were noted.[17] Where significant interactions were found, special contrasts were constructed to identify their precise source.

RESULTS

Smoking Prevalence

Percentages of the total sample who were nonsmokers, experimenters, or regular smokers at each grade level by sex are given in Table 1. This table gives changes in the percentage of smoking status for the total sample, as well as for boys and girls. The increase in the percentage of regular smokers over time is similar to results obtained from other surveys of similar-aged children.[19-21] The percentage of regular smokers increased (from 2.7% in 8th grade to 14.7% in 11th grade), while the percentage of nonsmokers gradually decreased (from 86.9% in 8th grade to 68.4% in 11th grade). The trend for the experimenters was less consistent, with the percentage fluctuating from year to year.

Trends similar to those for the total group were also found for the boys and for the girls. A downward trend for nonsmokers and an upward trend for regular smokers occurred across grades for boys and girls. However, contrary to some previous studies,[2,19,22] the percent-



Top, Self-reported smoking status of 65 regularly smoking 11th grade students during the 8th, 9th, and 10th grades. Center, Self-reported smoking status of 55 experimenting 11th grade students during the 8th, 9th, and 10th grades. Bottom, Self-reported smoking status of 303 nonsmoking 11th grade students during the 8th, 9th, and 10th grades.

Table 2.—Mean Values of Composite Variables for 11th Grade Nonsmokers and Regular Smokers During 8th to 11th Grades

Composite Variables	11th Grade Smoking Status	Mean Values by Grade			
		8th	9th	10th	11th
Association with friends who smoke	Nonsmoker	7.08	7.52	8.37*	8.92†
	Regular smoker	9.02	9.69	12.01	15.31
Parental attachment					
Paternal	Nonsmoker	11.54	11.00	11.06	11.15
	Regular smoker	10.12	8.29	8.82	9.74
Maternal	Nonsmoker	12.65	12.40	12.59*	12.65
	Regular smoker	10.86	9.40	11.37	11.20
Parental supervision	Nonsmoker	6.59	6.45	6.36*	6.32
	Regular smoker	5.66	4.91	5.89	5.44
Extracurricular activity	Nonsmoker	4.55	5.48	5.76	5.19†
	Regular smoker	3.98	4.18	5.03	3.69
Academic involvement	Nonsmoker	7.47	7.90	8.50	8.39†
	Regular smoker	6.46	5.94	7.48	6.28
Effects of smoking					
Negative	Nonsmoker	21.43	21.83	21.71	21.65†
	Regular smoker	19.43	18.95	18.49	16.06
Positive	Nonsmoker	13.92	13.91	14.00*	13.93†
	Regular smoker	14.52	14.43	15.81	17.20

*Significant interaction for the 9th to 10th grade comparison ($P<.05$).
†Significant interaction for the 10th to 11th grade comparison ($P<.05$). No significant interactions were found for the 8th to 9th grade comparison.

age of boys who were regular smokers was higher than the percentage of girls who were regular smokers at each grade. The difference in percentage of regular smokers was greatest in the 11th grade, where 16.9% of the boys and 12.6% of the girls were smoking regularly.

Change in Smoking Status

To explore further how and when changes in smoking occur, subjects categorized as nonsmokers, experimenters, and regular smokers in 11th grade were reclassified based on their smoking status in 8th, 9th, and 10th grades. This reclassification of smoking status over time is displayed in the Figure.

The top of the Figure shows the self-reported smoking status of 11th grade regular smokers when they were in the 8th, 9th, and 10th grades. The percentage of adolescents who were regular smokers almost doubled from one grade to the next. Of the 65 subjects who were regular smokers in 11th grade, 10.8% reported regular smoking in 8th grade, 23.1% in 9th grade, and 44.6% in 10th grade. There were 16.9% of the 11th grade regular smokers who were experimenters in 8th grade, 20.0% in 9th grade, and 10.8% in 10th grade. The trend for nonsmoking was 66.2% in 8th grade, 55.4% in 9th grade, and 43.1% in 10th grade.

The center of the Figure shows the 8th through 10th grade smoking patterns for adolescents who were experimenters in 11th grade. Of those students experimenting in 11th grade, 89.3% were nonsmokers in 8th grade, 83.9% in 9th, and 76.8% in 10th. A much smaller percentage of these 11th graders were experimenting in previous years: 7.1% in 8th grade, 14.3% in 9th grade, and 17.9% in 10th grade. There was a small group of experimenters in the 11th grade who had smoked more frequently in the lower grades; 5.4% of 11th grade experimenters reported being regular smokers in the 10th grade, whereas 1.8% were regular smokers in the 8th and 9th grades, respectively.

The 8th, 9th, and 10th grade smoking status of adolescents who reported being nonsmokers in 11th grade is displayed in the bottom panel of the Figure. More than 90% had been nonsmokers in each of the earlier grades. Only a small percentage of 11th grade nonsmokers (4.6% to 6.9%) had experimented with cigarettes earlier, and few (1.0% to 2.6%) reported being regular smokers in the earlier grades.

Factors Related to Change in Smoking Status

To assess whether the shift in smoking status was associated with a shift in the values of the predictor variables, we examined the change in the values of each variable for 11th grade nonsmokers and regular smokers as they advanced through the 8th, 9th, 10th, and 11th grades. Only those variables that provided a significant contribution to 11th grade smoking status were examined. Parental smoking did not provide a statistically significant contribution to the prediction of 11th grade smoking in any of the discriminant analyses. Thus, it was dropped from all subsequent analyses.

A 2×4 MANOVA was conducted to examine the interaction between 11th grade smoking status and the change of each variable from year to year. The results of this analysis are given in Table 2. Table 2 displays the means of the 11th grade regular smokers and nonsmokers on each measure for each of the 4 years, as well as the significance levels of the MANOVA tests of the interaction between grade and smoking status. Only the significant interactions are noted. No significant interactions were found when comparisons were made between the 8th and 9th grades. In addition to examining the significant interactions, an analysis of variance was used to test the differences between nonsmokers and regular smokers on each variable in the 8th, 9th, 10th, and 11th grades. Of the 32 comparisons, 26 were statistically significant at $P = .05$. Those variables for which there was no significant difference between the two groups were attachment to mother (10th grade), attachment to father (8th grade), parental supervision (10th grade), positive effects of smoking (8th and 9th grades), and extracurricular activity (8th grade). An examination of the mean scores and the pattern of interactions showed the following.

Association With Friends Who Smoke.—Eleventh graders who smoked not only had the tendency to associate with other smokers more than nonsmokers while they were in 11th grade but they also had this tendency in the 8th grade, when most of them were not smoking. In addition, regular smokers and nonsmokers steadily increased their association with friends who smoke throughout their school years. However, beginning in 9th grade, this increase was far more rapid for those who became regular smokers than those who remained nonsmokers. This latter phenomenon is indicated both by the significant interactions and by the mean values of each variable.

Attachment to Father and Mother: Parental Supervision.—The data on parental supervision and attachment to father and mother showed that the adolescents who reached 11th grade without becoming regular smokers tended to have closer relationships with their parents and felt more closely supervised by their parents, even as far back as 8th grade. Although significant overall changes in the degree of attachment and supervision from year to year were noted, the pattern of those changes was not markedly different for regular smokers and nonsmokers. Both groups, for example, seemed to develop some alienation from parents between the 8th and 9th grades but seemed to recover from it by the 10th and 11th grades. The important point to note in this part of Table 2 is that the regular smokers, as a group, consistently indicated that they were less attached to and less supervised by their parents.

Table 3.—Standardized Discriminant Function Coefficients for Variables Included in Each Analysis

Grade	Significant Variables	Standardized Coefficient
8th	Association with friends who smoke	.31
	Smoking status	.60
	Association with friends who smoke (failure to reply)*	.50
	Smoking status (failure to reply)*	.58
9th	Association with friends who smoke	.17
	Smoking status	.64
	Attachment to mother	−.35
	Negative effects	−.32
10th	Extracurricular activity	−.05
	Association with friends who smoke	.21
	Smoking status	.87
	Attachment to father	−.28
	Smoking status (failure to reply)*	.23
11th	Positive effects	.41
	Negative effects	−.47
	Association with friends who smoke	.57
	Academic involvement	−.20
	Association with friends who smoke (failure to reply)*	−.08

*Missing responses on this variable were significantly related to 11th grade smoking status.

Extracurricular Activities and Academic Involvement.—The results for the measures of extracurricular activities and academic involvement were similar. Eleventh grade nonsmokers, throughout the 4 years, consistently were more involved in extracurricular activities and more academically oriented. A positive change on both measures for regular smokers and nonsmokers was noted when they were in 9th or 10th grade, followed by a sharp negative change for regular smokers when they reached 11th grade, suggesting a lack of interest in school-related activities for this group then. The sharper drop for regular smokers than nonsmokers accounted for the smoking-by-grade interaction between the 10th and 11th grades. The most relevant finding on these measures was that, as early as 8th grade, students who began smoking regularly by the time they reached the 11th grade tended to be less academically oriented and less involved in extracurricular activities.

Perceptions of Positive and Negative Effects of Smoking.—Differences between the 11th graders who were nonsmokers and those who were regular smokers were detectable as early as the 8th grade, even before most of them had begun smoking. The students who became regular smokers in 11th grade consistently had more positive opinions and less negative opinions about cigarette smoking throughout the 8th, 9th, 10th, and 11th grades. The opinions of 11th grade regular smokers, especially when they reached the 10th and 11th grades, became even more positive about cigarette smoking, thus widening the opinion gap between regular smokers and nonsmokers. The change in perceptions of the regular smokers accounted for the interactions on these two measures between the 9th and 10th grades and between the 10th and 11th grades.

Risk Factors for Smoking

The analysis of variance of these data suggests that the risk factors associated with adolescent smoking vary over

Table 4.—Discriminant Analysis Classification Results: Smoking Status in 11th Grade as Predicted by Significant Variables in Grades 8 to 11*

Grade of Predictive Variables	Actual Smoking Status in 11th Grade	11th Grade Actual No. of Cases	Predicted 11th Grade Smoking Status, No. (%)		
			Nonsmokers	Experimenters	Regular Smokers
8th	Nonsmoker	303	205 (67.7)	59 (19.5)	39 (12.9)
	Experimenter	55	31 (56.4)	16 (29.1)	29 (14.5)
	Regular smoker	65	21 (32.3)	15 (23.1)	29 (44.6)
9th	Nonsmoker	303	210 (69.3)	70 (23.1)	23 (7.6)
	Experimenter	55	20 (36.4)	26 (47.3)	9 (16.4)
	Regular smoker	65	21 (32.3)	14 (21.5)	30 (46.2)
10th	Nonsmoker	303	211 (69.6)	71 (23.4)	21 (6.9)
	Experimenter	55	15 (27.3)	30 (54.5)	10 (18.2)
	Regular smoker	65	16 (24.6)	13 (20.0)	36 (55.4)
11th	Nonsmoker	303	227 (74.9)	58 (19.1)	18 (5.9)
	Experimenter	55	16 (29.1)	28 (50.9)	11 (20.0)
	Regular smoker	65	3 (4.6)	12 (18.5)	50 (76.9)

*Total cases correctly classified were as follows: 8th grade, 250 (59.1%); 9th grade, 266 (62.9%); 10th grade, 277 (65.5%); and 11th grade, 305 (72.1%).

time. This finding was explored further with discriminant analyses to identify the variables that provide the best discrimination between the 11th grade nonsmokers, experimenters, and regular smokers at different grade levels.

The results of the discriminant analyses are given in Tables 3 and 4. Table 3 gives the standardized coefficients for variables included in each of the analyses. The optimum test of the predictive validity of these standardized coefficients would be to use them to predict the smoking behavior of a totally new sample of adolescents. In the absence of such a sample, we believe that examining the accuracy with which the variables in Table 3 can classify the subjects used in this study provides a reasonable estimate of their validity, albeit a somewhat high estimate. Perhaps of equal importance, seeing the percentage of adolescents who can be correctly classified in this way probably clarifies the power of these predictors better than knowing only the standardized coefficients.

The discriminant analysis of the 8th grade variables yielded four statistically significant variables. Smoking status in the 8th grade was the best single predictor, followed by association with friends who smoke. The nonresponse indicator variables for smoking status and association with friends who smoke were the next best predictors, indicating that subjects who failed or refused to answer these items in 8th grade were more likely to smoke in 11th grade. Association with friends who smoke in the 8th grade was positively related to one's smoking status in 11th grade.

Similar results were obtained for the 9th grade analysis, with four variables found to be significant. Both the smoking status and association with friends who smoke variables were significant positive predictors of 11th grade smoking status. The negative effects variable was a significant negative predictor, suggesting that those 9th grade adolescents who viewed cigarette smoking as having fewer negative effects were more likely to smoke in the 11th grade. Attachment to mother was also a significant negative predictor, suggesting that adolescents who had a poorer relationship with their mothers in the 9th grade were more likely to be smoking in the 11th grade.

Of the five significant 10th grade variables, smoking status and association with friends who smoke were the two strongest predictors of 11th grade smoking status. Adolescents' ratings of the importance of athletics and other extracurricular activities and their attachment to fathers were significant negative predictors, suggesting that students who valued being involved in extracurricular activities and those with positive paternal relationships were less likely to be regular smokers. The nonresponse indicator variable for smoking status was a significant positive predictor of 11th grade smoking status.

Five variables were found to be significant predictors in the 11th grade analysis. As in previous analyses, association with friends who smoke was a significant positive predictor of 11th grade smoking status. The positive and negative effects variables were also strong predictors of 11th grade smoking, which supports previous findings from research investigations conducted in this school district,[23] suggesting that smokers are more likely than their nonsmoking peers to believe cigarette smoking has positive attributes. Academic involvement was a significant negative predictor, supporting previous research findings[9,11,12] that suggest that adolescents who are regular smokers do more poorly in school. The nonresponse indicator variable for association with friends who smoke was also included in the analysis. It was negatively related to 11th grade smoking status.

Several variables that were either excluded from the analyses or did not contribute significantly to 11th grade smoking status deserve mention. One variable that provided a minor contribution was parental supervision. A possible reason for its minor contribution is the inclusion of the attachment to father/mother variables. The significant contribution of each of these two variables may have reduced the apparent influence of parental supervision, because parental supervision and attachment to parents are likely interrelated. Hence, when one enters the equation, the others drop out because the variance they might explain is already explained by the one that is entered. Variables examining the influence of parental smoking on adolescent cigarette use were initially included in the analyses but were dropped owing to their failure to add significantly to the prediction of 11th grade smoking status. There are two possible reasons why parental smoking was not found to be a significant predictor of 11th grade smoking status. The most likely is that the other variables included in our analyses overshadowed the influence of parental smoking on adolescent cigarette use. When compared with other variables that influence adolescent smoking (eg, friends who smoke, academic involvement), the influence of parental smoking became negligible. Multivariate statistical analyses in other investigations of variables influencing adolescent cigarette use have also shown parental smoking to be a poor predictor.[6,26] Second, those investigations that have found parental smoking to be meaningful to adolescent cigarette smoking have tended to be cross-sectional in design. A significant relationship between parental smoking and adolescent smoking status might have been found in this investigation had we conducted cross-sectional rather than longitudinal analyses. Thus, it is possible that parental smoking has a short-term effect on adolescent cigarette use, but that the long-term predictive effects of parental smoking are negligible.

The significant variables from each analysis were used to classify students as nonsmokers, experimenters, or regular smokers. The classification results of the discriminant analyses are reported in Table 4. Using the four significant variables from the 8th grade analysis (Table 3), 250 (59.1%) of the 423 cases were correctly classified. The number of cases correctly predicted is located in the diagonal of each prediction set in Table 4: 67.7% of the nonsmokers, 29.1% of the experimenters, and 44.6% of the regular smokers were classified correctly into their actual groups in 11th grade from these 8th grade variables. The discriminant analysis of the four significant 9th grade variables resulted in 266 (62.9%) of 423 cases being correctly classified: 69.3% of the nonsmokers, 47.3% of the experimenters, and 46.2% of the regular smokers were correctly classified. The discriminant analysis of the 10th grade data was based on five significant variables. Two hundred seventy-seven (65.5%) of the 423 subjects were correctly classified using these variables: 69.6% of the nonsmokers, 54.5% of the experimenters, and 55.4% of the regular smokers were correctly classified. For the 11th grade discriminant analysis, the prediction of group membership was based on five significant variables. Of the 423 students, 305 (72.1%) were correctly classified using these variables. As can be seen, 74.9% of the nonsmokers were correctly classified, along with 50.9% of the experimenters and 76.9% of the regular smokers.

COMMENT

Our data suggest that efforts to prevent cigarette smoking should begin early. A large portion of the children who are at risk for cigarette smoking may be identified by their attitudes, peer and parental relationships, and involvement in school activities. Parents, teachers, and physicians should be particularly aware of these smoking risk factors.

In the cohort of children described in this study, smoking gradually increased throughout adolescence, with about 17% of boys and 13% of girls smoking regularly by 11th grade. In addition, experimenting with smoking occurred more frequently as adolescents matured. Those who smoked regularly tended to have certain risk factors that distinguished them from their nonsmoking peers. Many of these distinguishing characteristics were present as early as 8th grade (before most of them adopted regular smoking). These factors included previous smoking status, close association with friends who smoke, less attachment to parents, poor school performance, less involvement in extracurricular school activities, and fewer negative and more positive perceptions of cigarette use. Of these factors, previous smoking status and association with friends who smoke were the major predictors of an adolescent's smoking by the time he or she reached the 11th grade. This suggests that these factors can be used to identify at an early age adolescents who are most likely to smoke.

Given the small number of variables in the discriminant equations, and the fact that only about one third of these adolescents would be correctly classified by chance, correctly classifying 59% to 72% using these equations is good evidence of the importance of these variables in predicting, if not to some extent explaining, smoking behavior. These results also demonstrate, though, that we have not yet identified all of the variables that explain smoking behavior. Thus, additional research is needed to identify other potential causes. Additional research is also needed to establish the validity of these findings with other populations. While these observations have been made on a predominantly white, middle-class population, other studies, summarized below, indicate the findings and implications are generalizable.

Previous research has suggested that the peer group is perhaps the strongest and most consistent influence on adolescent smoking.[3,7,8] In our analyses, the strong influence of the peer group on cigarette use seemed to have the greatest influence on cigarette use across time. Our data showed that 11th graders who smoked regularly had more friends who smoked than 11th graders who did not smoke, even when they were in the 8th grade (when most of them were not smoking). The increase over time in association with friends who smoke is greater for those who become regular smokers than for those who continue to be nonsmokers.

Regularly smoking adolescents tend to be less successful in school and do not participate in school-related activities.[10] This generalization is supported by the significant inverse relationship between 11th grade smoking status and participation in extracurricular activities and academic involvement. These findings support previous investigations that suggest that adolescents who smoke are more likely to be dissatisfied with traditional forms of socialization, such as school and family, and tend to form relationships with peers who also participate in less conventional forms of behavior.[10] One possible explanation for this phenomenon is that these adolescents are attempting to disassociate themselves from adolescence.[12] Those adolescents who do not participate in school activities, or who do poorly in school, are particularly likely to seek peer groups outside "supervised" activities.

Although a significant relationship was found between perceptions of the negative effects of smoking (9th and 11th grade analyses) and 11th grade smoking status, and between perceptions of the positive effects of smoking (11th grade analysis) and 11th grade smoking status, we found that nonsmokers and regular smokers have negative perceptions about smoking when they are in the 8th grade. The nonsmokers retain negative perceptions throughout the 4 years, while the regular smokers' perceptions become consistently more positive.

Positive parental relationships and concern about adolescents are particularly important for adolescents as a constraint on smoking. Support for this generalization comes not only from this study but also from previous investigations that suggest that the quality of the relationship between adolescents and their parents plays an important role in the adolescents' development.[8,9] These investigations suggest that a poor relationship within the family setting tends to weaken the bond between child and parent, thus reducing the constraint that this relationship places on smoking behavior. Our findings, in which attachment to mother and attachment to father were associated with less regular smoking, agree with these investigations. Attachment to mother, attachment to father, and parental supervision all tended to change over time, but nonsmokers as a group had consistently higher levels of attachment to parents and parental supervision than regular smokers throughout the 4 years.

The data presented herein indicate that factors associated with adolescents' cigarette use begin to exert their influence at a young age (at 12 to 13 years of age). For this reason, parents, teachers, and physicians should increase their awareness of the risk factors at any early age, prior to the onset of smoking. These findings suggest that parents, teachers, and physicians could promote nonsmoking behavior by providing opportunities for adolescents who smoke to associate with nonsmoking peers in daily social and school-related activities. Innovative efforts are needed by schools and other social agencies to attract disaffected adolescents into positive peer groups. These efforts should focus on developing activities in a nonsmoking atmosphere where adolescents can succeed in feeling part of a mainstream group. Physicians, teachers, and parents should emphasize to adolescents the physiologic and social consequences of smoking.[24,25] Emphasizing such characteristics as clothes that smell from cigarette smoke, stained teeth, and bad breath might help to discourage some adolescents from smoking. Finally, parents should be encouraged to play an active role in their children's academic and social activities and build time into their daily schedules for more interaction with their children at home.

This research was supported by grant R01-HL32847 and SCOR in Atherosclerosis HL-14230 from the National Heart, Lung, and Blood Institute, Washington, DC.

Additional information can be obtained from Dr Reimers, Children's Memorial Hospital, 8301 Dodge St, Omaha, NE 68114.

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Special Feature

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Ahmed H. Al-Salem, FRCSI, FICS, Saleem Khwaja, FRCS *(Contributors)*;
Beverly P. Wood, MD *(Section Editor)*

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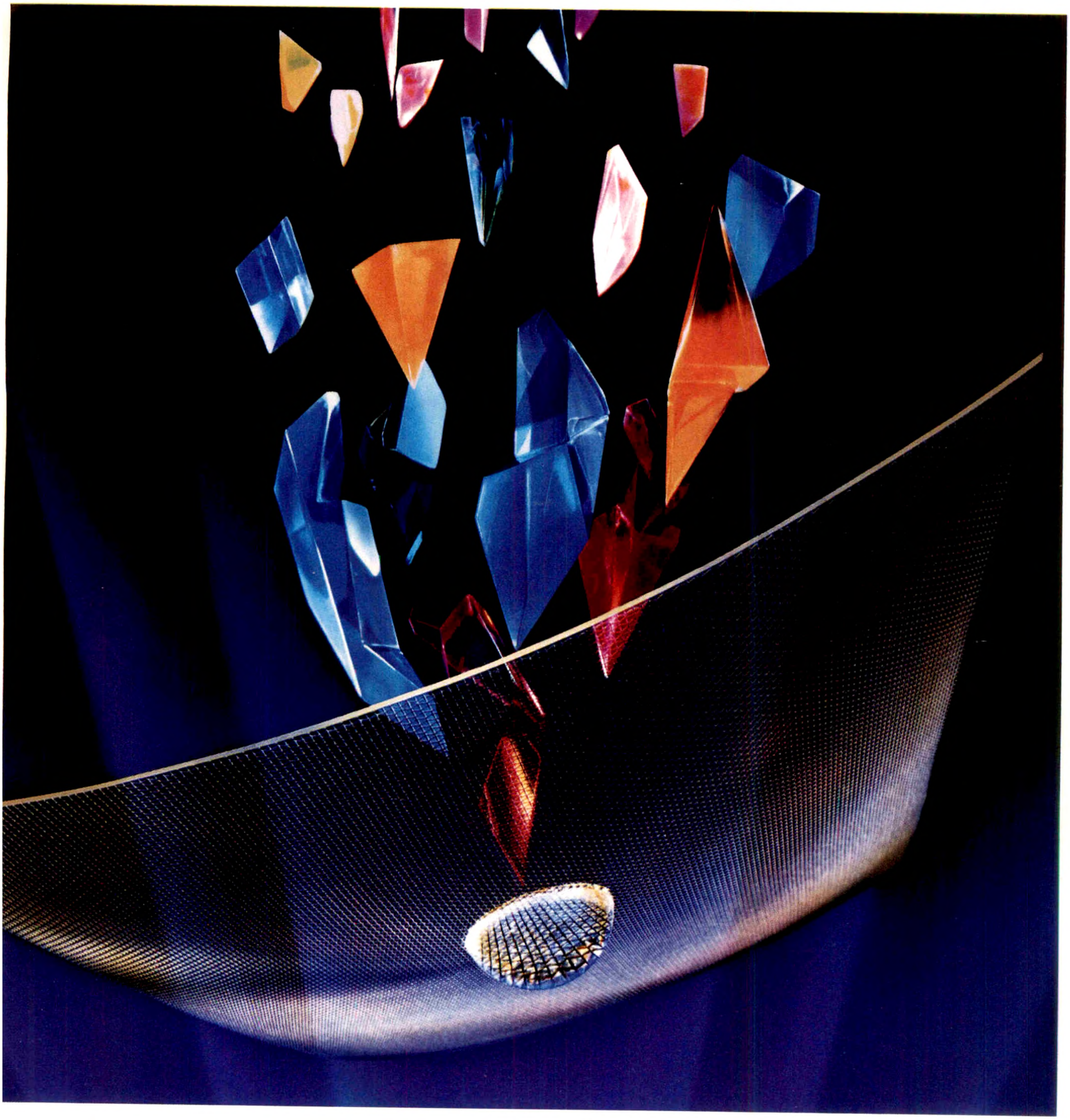

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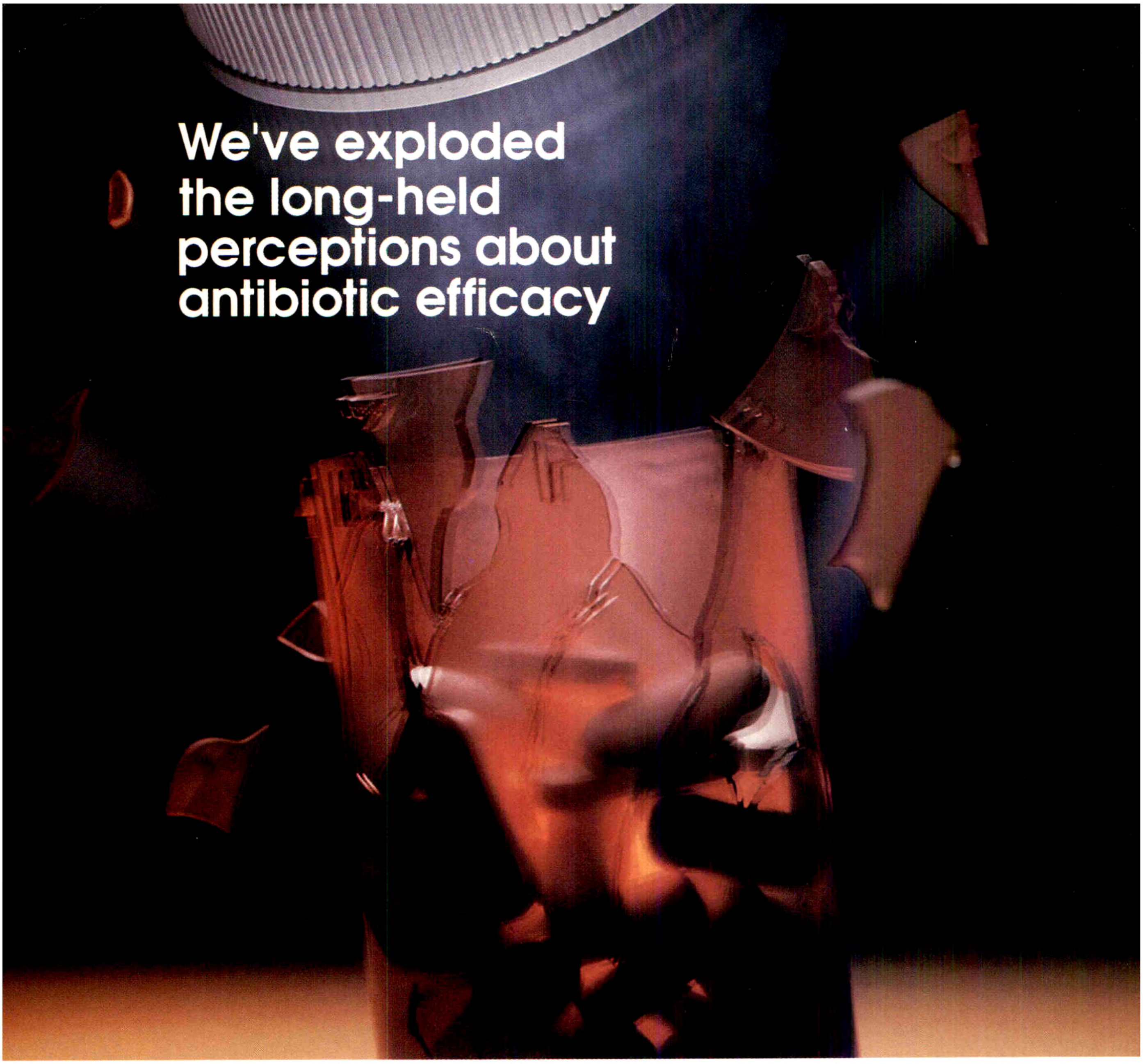
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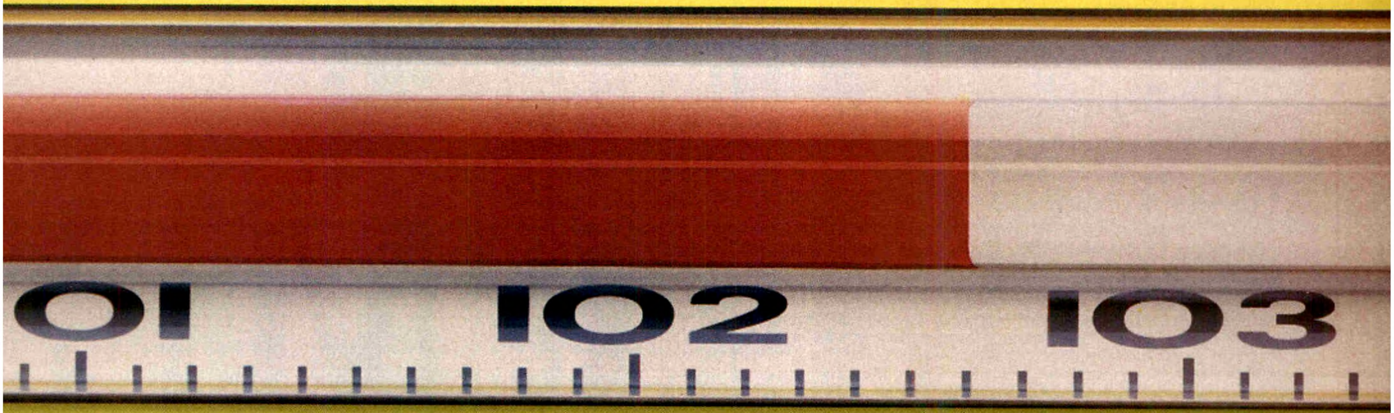

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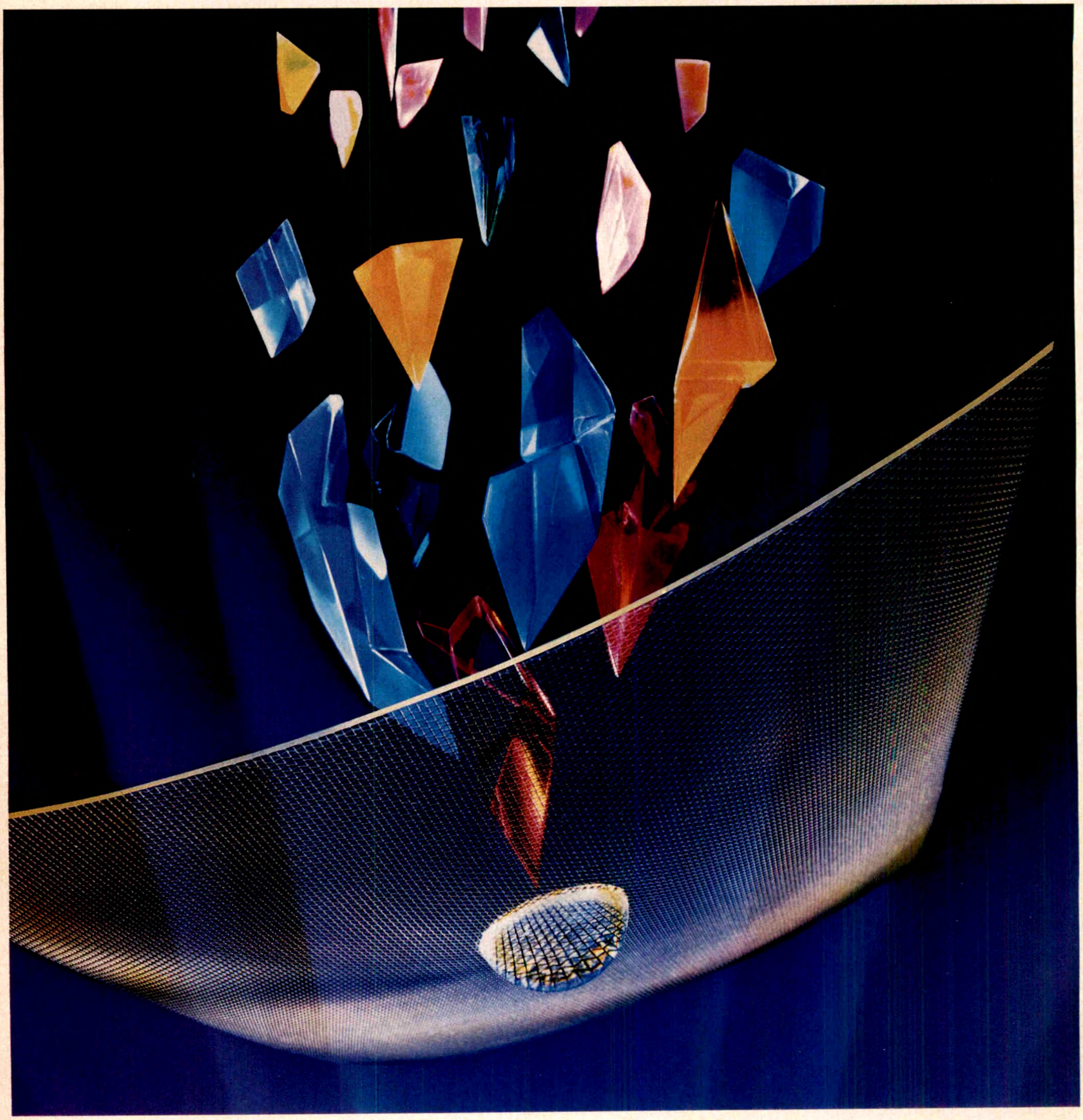

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Articles

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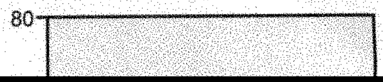
Prevalence of Smoking During Pregnancy According to Various Maternal Characteristics



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cents has increased in recent years.[4,17,24] Our results suggest that little headway has been made during the last 5 years toward altering the smoking behavior of teenagers who become pregnant. It may be that cessation programs are not working or are not available to those most in need of them. Alternatively, it may be that teenagers who are or will become pregnant are less amenable to cessation programs. Certainly, among the high-risk groups that need extra attention are the unmarried pregnant teenagers, who, in this study, had a smoking rate above 42%, as well as the unmarried nonpregnant teenagers who are sexually active and attending family planning clinics or school-based clinics.

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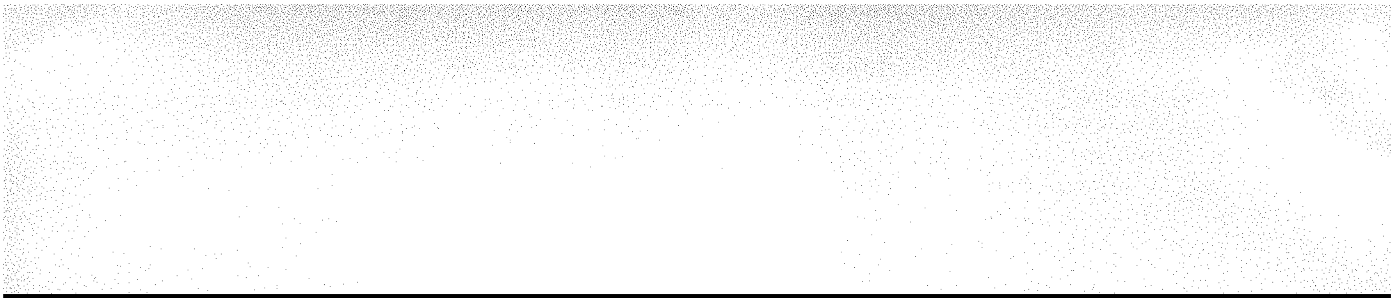

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Patient 5.—A female infant was born after 24 weeks gestation and weighed 640 g. Her weight was between the 10th and 25th percentiles for her gestational age. Initial physical examination showed no dysmorphic features. She was intubated for HMD from birth, initially via an oral endotracheal tube, then via a nasal endotracheal tube from day

Birth Factors and Intubation						
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Gestational age at birth, wk	31	27	25	24	24	35
Birth weight, g	1780	915	620	700	640	1580
No. of days						

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Fig 3.—Anteroposterior and lateral photographs of patient 3 at postnatal age 4.0

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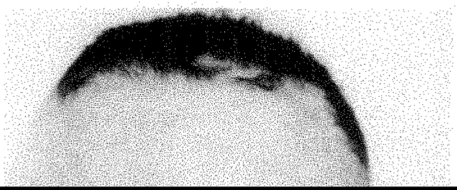

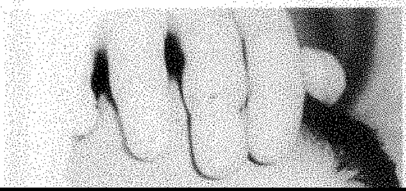

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Cytomegalovirus Infections in Pediatric Liver Transplantation

Susan M. King, MD; Martin Petric, PhD; Ric Superina, MD; Nancy Graham, RN;
Eve A. Roberts, MD

• **From 1986 to 1989, 26 consecutive**

drome.[2] Although the majority of the

the first 4 weeks after transplantation; then,

[redacted]

leukopenia (white blood cell count $<4 \times 10^9$/L), thrombocytopenia (platelet count, $<100\,000 \times 10^9$/L), or atypical lymphocytes (>0.03); (3) localized disease-tissue invasion of a single organ determined histopathologically, by culture of CMV from the tissue, or by clinical evidence of retinitis; and (4) disseminated disease-tissue involvement of two or more sites or tissue involvement of one site and CMV isolation in peripheral blood cells.

Management of CMV Infections

Prophylaxis for prevention of CMV evolved throughout the period under review. All seronegative patients (R −) received only blood and blood products screened and

Cytomegalovirus Infections and Disease in Pediatric Liver Transplant Recipients*

CMV Serostatus Pretransplantation					
Recipient	**Donor**	**No. of Cases**	**CMV Infection**	**CMV Disease**	**Fatal CMV**
−	−	12	1	1	0
+	−	4	4	2	0
−	+	4	4	3	3
+	+	6	5	3	3
Total	. . .	**26**	**14**	**9**	**6**

*CMV indicates cytomegalovirus; minus sign, negative; and plus sign, positive.

in the range of 100 to 400 μg/L measured by

had evidence of CMV infection, except

[redacted]

tion with a viral syndrome that resolved without antiviral therapy.

CMV Disease and Immunosuppressive Therapy

The mean number of days of adminis-

lence of CMV is lower than that in adults.

It is generally believed that antecedent CMV infection protects against severe CMV disease. However, severe CMV disease in liver transplant recipi-

dures such as bronchoalveolar lavage, lung biopsy, and bowel biopsy are required in most cases to confirm the diagnosis of CMV disease. The indications for these procedures may differ between transplant programs, which

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Saunders Co; 1987:1558-1565.

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GASTROINTESTINAL SYSTEM AND

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gist/psychiatrist, and a genetic counsel-

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Table 1.—Correlation of Impetigo Lesion Appearance With Culture Results*

Lesion Appearance	Organism

were unavailable for follow-up. Patients ranged in age from 5 months to 15 years, with a median age of 3 years, and 25th and 75th percentiles of 2 years and 6 years, respectively. Forty-one were

tant SA (two from pustular lesions and two from honey-crusted lesions), one had produced penicillin-resistant SA and GABHS (from pustular lesions), and one had produced no growth (from

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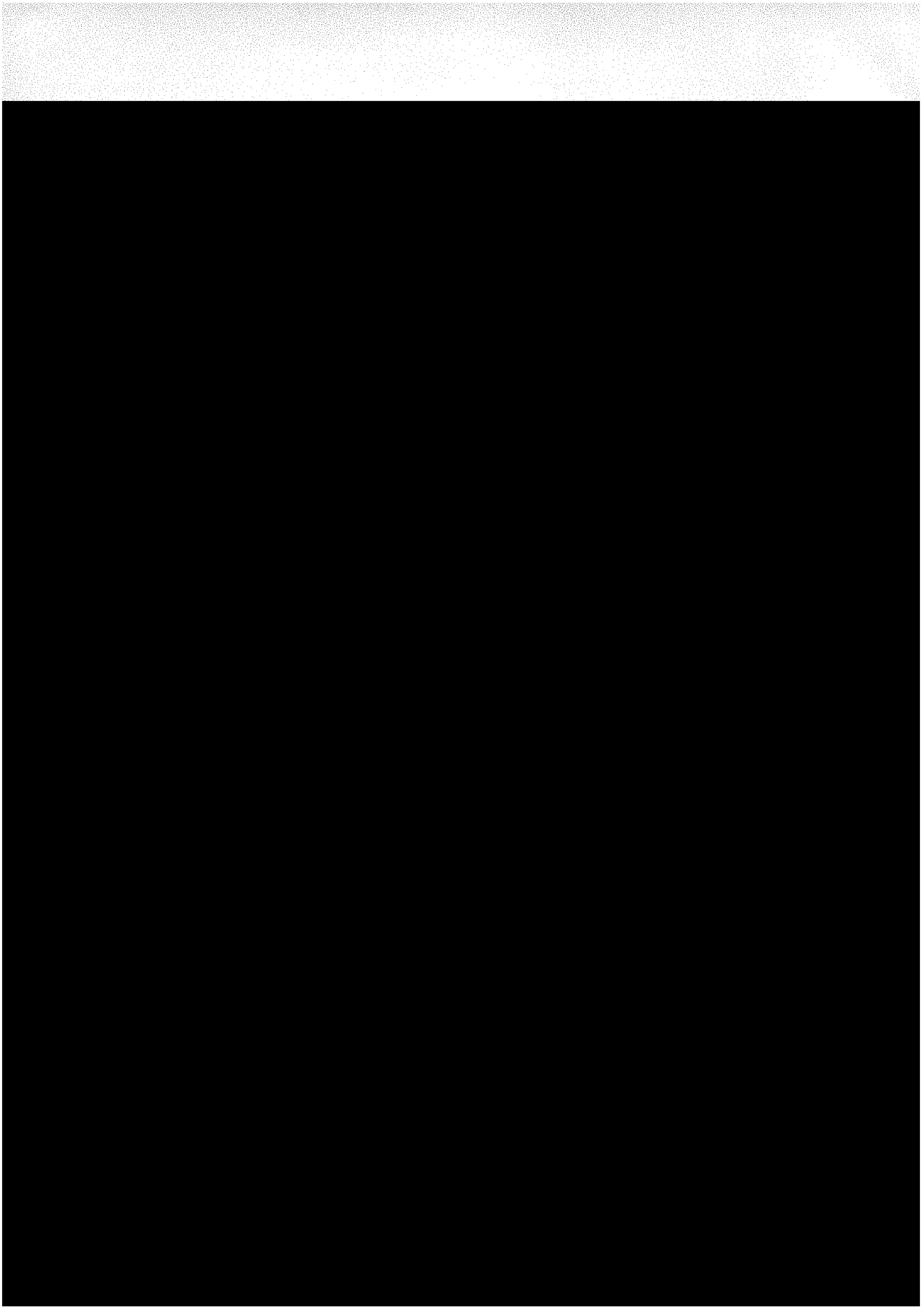
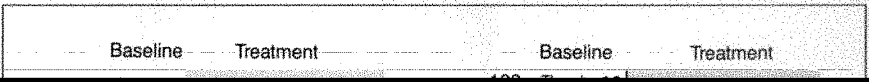


maintain a dispassionate, nonreactive attitude toward thumb-sucking throughout the study. Of 39 potential participants, eight



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(baseline means: child 1, 60%; child 2, 63%; child 3, 67%; child 4, 69%; child 5, 55%; child 6, 55%; child 7, 38%; and child 8, 25%) to zero levels, maintained at 3 and 6 months in all children. Initial high levels of object attachment in seven of the children (baseline means: child 1, 30%; child 2, 63%; child 3, 35%; child 4, 51%; child 5, 40%; child 6, 55%; and child 7, 32%) also reduced to zero levels. The parents reported the children just seemed to lose interest in their objects. In child 8, however, baseline levels of attachment increased during treatment and follow-up.

COMMENT

The results of this study extend the literature by replicating previously obtained treatment results[15,16] in a new population: thumb-sucking children with strong attachment to an object. The treatment, a taste- and reward-based combination, eliminated thumb-sucking in all eight children

tain to whether successful treatment of thumb-sucking leads to increases in other related habits.

Concerns that such increases may occur are based on the putative important function served by thumb-sucking.[11,19] Relevant to these concerns are the data from child 8 (Figure). This child broke his arm during the first week of treatment during which he had already stopped sucking his thumb. The parents reported he talked with them shortly after his accident about resuming sucking. They suggested he use his blanket instead—and he agreed. He did not return to thumb-sucking for the duration of the study but both his data (and his parents' report) show his attachment to his blanket increased. Thus, this child's reliance on his blanket as a substitute for his thumb provides partial support for concerns that thumb-sucking fulfills an important function for some children. In place of it, these children may turn to other habits.[11,19]

attachment objects. Thus, the function fulfilled by thumb-sucking and attachment appeared to be unimportant for them. Nevertheless, a more definitive answer about the importance of thumb-sucking and related habits can be obtained only when a broader spectrum of behavior is studied. Thus, more research is needed.

In lieu of that research and in light of the present findings, two suggestions about thumb-sucking treatment can be made. First, when thumb-sucking appears to be fulfilling an important function, it should not be treated.[8,19] A partial list of children for whom the function of thumb-sucking may be important includes any child who is sick, disturbed, grieving, injured, adamantly opposed to treatment, or younger than 5 years.[8,18,19] Second, when thumb-sucking is an empty habit, treatment is appropriate even if habitual attachment is concurrently practiced. Additional guidelines for treatment are available

[redacted]

Genital and Anal Conditions Confused With Child Sexual Abuse Trauma

Jan Bays, MD, Carole Jenny, MD

• **Examination of a child with genital or anal disease may give rise to suspicion of sexual abuse. Dermatologic, traumatic, infectious, and congenital disorders may be confused with sexual abuse. Seven children referred to us are representative of such confusion.**

(*AJDC*. 1990;144:1319-1322)

When genital or anal disease occurs, the health care provider must perform a careful examination and consider diagnoses other than sexual abuse, especially when the child volunteers no history of abuse. Ten percent to 25% of children are sexually abused before age 18 years.[1] With increasing awareness of this problem, physicians are being called on more frequently to examine children for signs of possible abuse. A diagnosis of sexual abuse may have serious consequences for the child, family, and suspected offender. We will review the existing literature on conditions mistaken for injuries due to child sexual abuse and present cases of seven children referred to us.

PATIENT REPORTS

PATIENT 1.—A 6-year-old girl was referred for a sexual abuse examination after her pediatrician noted fresh vaginal bleeding and genital bruising and made a report of suspected abuse. On the day of the examination, the child had returned to her divorced mother after a visit with her father.

She had subepidermal bleeding over the left side of the clitoris, the left labium minus, and the left wall of the introitus. There was a 2-cm ruptured bulla in the posterior fourchette to the right of the midline. The hymen was normal. There was a slight decrease in the pigmentation of the skin surrounding the genitalia. There were two superficial fissures of the anal verge. The child was questioned in private and denied sexual abuse. She was referred to a dermatologist, who diagnosed lichen sclerosus confirmed by biopsy (Fig 1). Treatment with topical corticosteroid decreased the friability of the skin around the vagina and anus.

PATIENT 2.—A 5-year-old girl was referred by her private pediatrician with a complaint of intermittent vaginal bleeding. Over a 15-month period, the child had had 11 episodes of small amounts of red or brown blood on her underwear or on toilet paper. She had occasional episodes of dysuria. A vaginal culture was positive for *Streptococcus pyogenes* on one occasion, but treatment with antibiotics did not stop the vaginal bleeding. Serum follicle-stimulating hormone, luteinizing hormone, and estradiol levels were normal on two occasions.

Genital examination revealed Tanner 1 female genitalia with a large, dilated, tortuous vein running from the top of the clitoris down through the right labium majus. The vaginal opening was completely hidden in hymen tissue, which was swollen and dark beefy red. There were a number of bright red, dilated blood vessels in the posterior fossa. The child was interviewed alone and denied sexual abuse. A magnetic resonance imaging scan of the pelvis was normal. Examination under anesthesia revealed a hemangioma of the entire vagina. There was no evidence of sarcoma botryoides or foreign body. No treatment will be undertaken unless significant bleeding occurs.

PATIENT 3.—A 7-month-old female infant was seen in an emergency department for high fever. The examining pediatrician found an area in the perineum that he thought might be due to an injury from sexual abuse. The child and her 2-year-old sister were placed into protective custody by the police. Three days later, the child was brought in for examination at a sexual abuse evaluation center. Genital examination revealed a vaginal opening hidden in light pink, redundant hymen tissue, which showed no evidence of trauma. Just below the rim of the posterior fourchette in the midline there was a deep red depression measuring 2 mm long and 1 mm deep. Under the colposcope, this depression appeared to be a congenital pit (Fig 2), which could be manipulated and stretched so that the increased vascularity in its depth blanched. The infant's sister had a normal genital examination, and both girls were returned to the custody of their parents.

PATIENT 4.—A 5-year-old girl was brought to the outpatient clinic for a genital injury. The child stated that she had been climbing on a stool at her grandmother's house and had fallen. A wooden leg of the stool had struck and injured her genitalia. She had experienced two episodes of dysuria and hematuria in the 4 hours since the injury occurred. Several clinic personnel expressed concern that the child might have been sexually abused.

Genital examination revealed a 2-cm laceration in the crease lateral to the right labium minus, with adjacent bruising (Fig 3). The hymen was normal. The child denied sexual abuse. No report of suspected abuse was made.

PATIENT 5.—A 2½-year-old boy told his mother that his "bottom hurt" on returning from day care. His physician diagnosed anal trauma, and a day-care worker was interviewed by the police after the child said, "Mark hurt me." After the child was examined at a child abuse center, the diagnosis of perianal streptococcal cellulitis was made (Fig 4). On further questioning, the child said the day-care worker had hurt him when he was wiped after toileting. The pain apparently occurred because of preexisting anal irritation from the infection.

PATIENT 6.—A 5-year-old girl was referred to a sexual abuse evaluation program because her pediatrician had noted that her clitoris was split. Examination revealed a complete cleft of the upper genital structures, including the clitoris, labia minora, and anterior urethral wall. The child denied trauma or sexual abuse. Normal uterus, ovaries, and kidneys were visualized on ultrasound examination. Voiding cystourethrogram was normal except for a 1.7-cm split in the pubic symphysis. The child was referred to a pediatric urologist with a diagnosis of

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From the Department of Pediatrics and Child Abuse Response and Evaluation Services, Emanuel Hospital, Portland, Ore (Dr Bays); and Department of Pediatrics, University of Washington School of Medicine, Seattle (Dr Jenny).

Reprint requests to Department of Pediatrics, Emanuel Hospital, 2801 N Gantenbein, Portland, OR 97227 (Dr Bays).

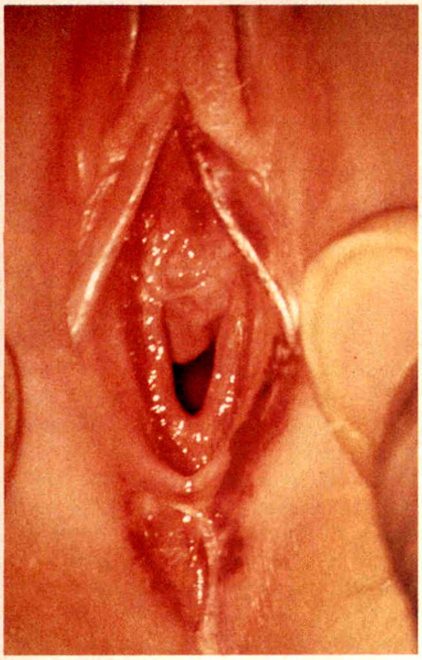

Fig 1.—Patient 1. Lichen sclerosus.

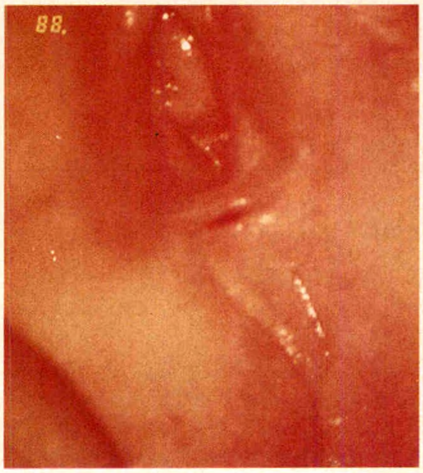

Fig 2.—Patient 3. Congenital pit of the perineal body.

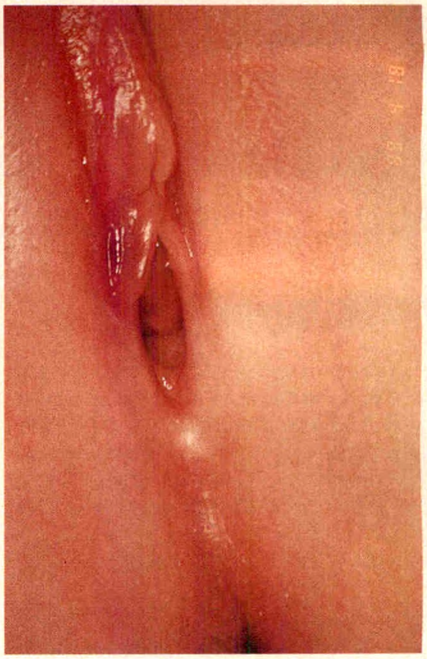

Fig 3.—Patient 4. Straddle injury adjacent to the right labium.

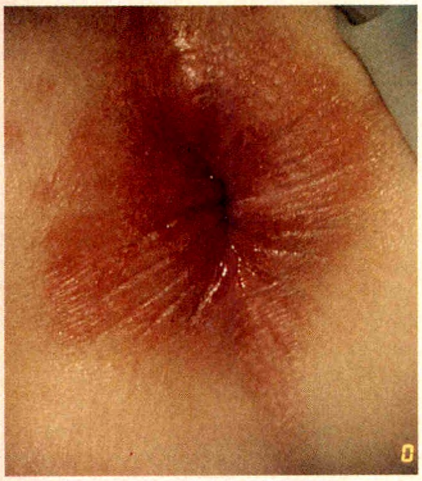

Fig 4.—Patient 5. Perianal streptococcal cellulitis.

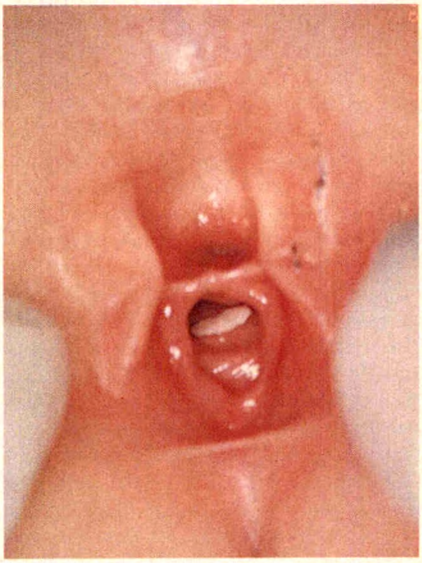

Fig 5.—Patient 6. Epispadius (incidental foreign body).

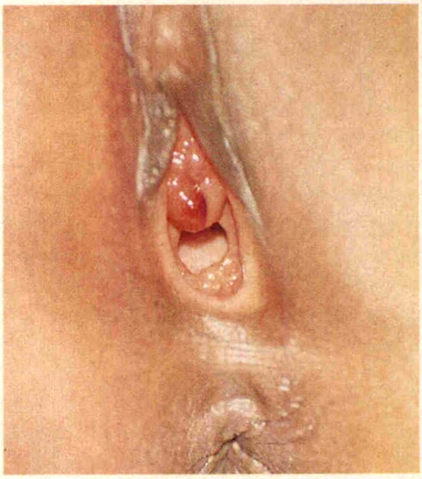

Fig 6.—Patient 7. Periurethral caruncle.

congenital epispadius (Fig 5).

Patient 7.—A 4-year-old girl was referred for possible sexual abuse when she complained of dysuria and had several episodes of hematuria after playing with older neighborhood children. The child and her playmates convincingly denied sexual abuse or sexual play when questioned by the patient's concerned mother and pediatrician. Genital examination revealed a hemorrhagic urethral caruncle (Fig 6). The child's symptoms resolved over 3 weeks with warm sitz baths and topical estrogen cream. A report of suspected abuse was not made.

COMMENT

Dermatologic Disorders

Erythema and excoriations of the genitalia are not signs specific to sexual abuse, as they may have many other common causes, including diaper dermatitis, poor hygiene, *Candida*, pinworms, and irritants such as bubble bath.[2,3] Increased pigmentation around the anus, although reported after chronic sexual abuse, is a common finding in nonabused children.[2] Bruises in the genital or anal area can raise suspicion of possible sexual abuse. Bruising confused with child abuse has been re-

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Parenchymal and Vascular Magnetic Resonance Imaging of

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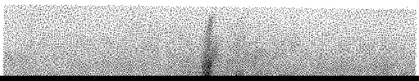

ing ECMO because of the ferromagnetic materials in the pump mechanism and

[redacted]

flow through the circle of Willis.[11-13] Post-ECMO xenon blood flow studies and digital intravenous angiography have demonstrated symmetric intracranial blood flow in these children.[23]

Magnetic resonance angiography also demonstrated good blood flow in the anterior and middle cerebral arteries bilaterally. The complete circle of Willis

[redacted]

sels widen in diameter coincident with body growth. Its limited field of view is adequate to assess flow in the circle of Willis and its branches. Doppler US, which is portable and can be used during ECMO, provides the most information about the direction and velocity of intracranial blood flow. However, a complete study is dependent on a patent fonta-

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13. Matsumoto JS, Babcock DS, Brody AS, Weiss RG, Pyckman FG, Hlyama D. Intracranial blood flow as measured with duplex sonography during ligation of the right common carotid artery for extracorporeal membrane oxygenation. *Radiology.* 1988;169(P):76.

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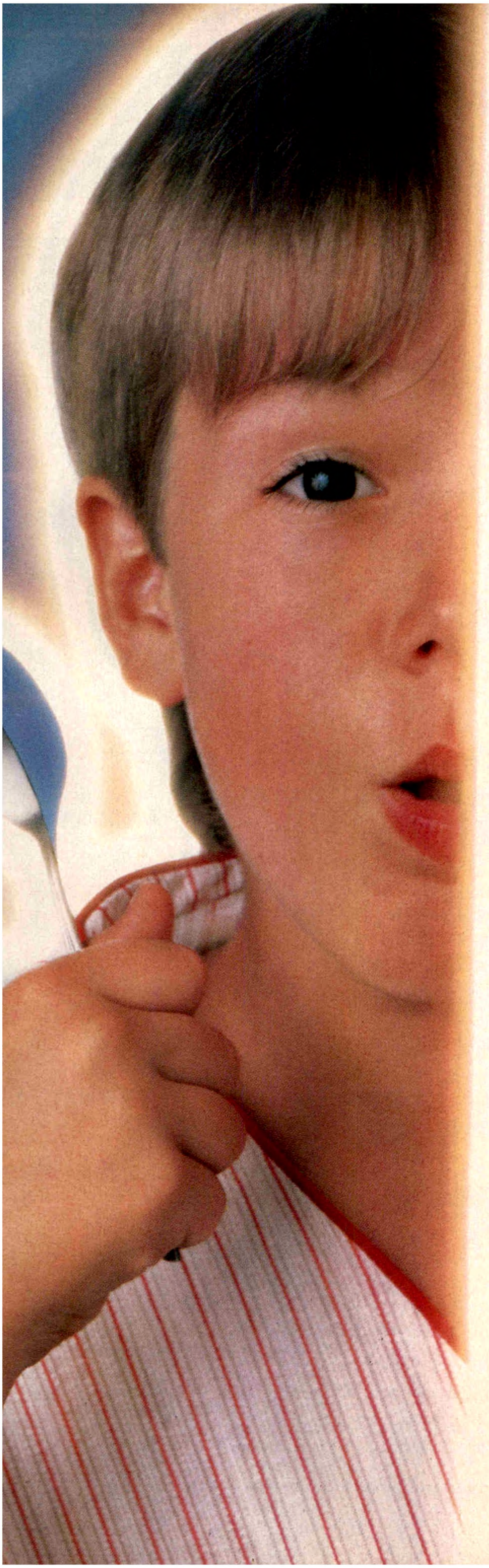

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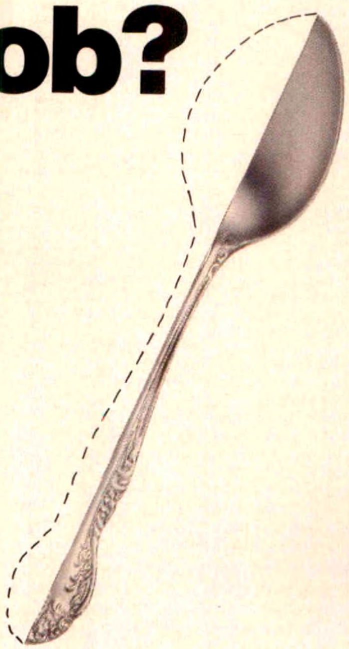

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Table 2.—Procedures Used by Residents in Diagnosing ADHD*

Procedure	Mean†	% "Frequently" or "Always"	% "Rarely" or "Never"
History from parent	4.6	98.3	0.8
History from teacher	4.5	97.5	0.0
Physical examination	4.4	83.1	8.5
Examination room behavior	4.3	86.1	3.3
Assessment of family functioning	4.0	71.3	3.5
Psychological testing	4.0	69.7	6.7
Teacher-completed rating scales	3.8	68.7	13.0

PGY-1 and PGY-2 ($P < .05$). Residents reported that they had limited experience in treating children with ADHD (mean number of current cases, two; SD, 4.6).

COMMENT

The pediatric trainees participating in this study reported the use of evaluation and treatment procedures for children with ADHD that approach current empirically based recommendations.

[redacted]

Table 4.—Professionals Consulted by Residents for ADHD Cases*

Professional	Mean†	% "Frequently" or "Always"	% "Rarely" or "Never"
Psychologist	3.6	61.8	11.9
Behavioral pediatrician	3.0	44.7	28.9
Neurologist	2.7	22.8	45.6

agnostic signs of ADHD from associated features such as learning problems and social difficulties, and most residents missed several diagnostic signs. Although placebo trials are often necessary to evaluate the effectiveness of stimulant medication,[18] more than 75%

[redacted]

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The Use of Anatomically Correct Dolls in the Evaluation of Sexually Abused Children

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White et al[1] compared 25 children suspected to have been victims of sexual

between sexually abused and non-abused children. Sivan et al[2] and Glasser

not prove or disprove abuse. Yates points out that the only way that the

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Lung Function in Children Following Empyema

Gregory J. Redding, MD; Lori Walund; Dean Walund, MD; Janet W. Jones, RPT;
David C. Stamey, RRT; Ronald L. Gibson, MD, PhD

• Spirometry was performed and response to exercise was measured in 15 children following recovery from empyema to evaluate the impact of pleural infection on subsequent lung function. Seven children underwent chest tube drainage; eight did not. The two groups were similar in age (mean ± SD, 6 ± 5 years), sex distribution, bacterial pathogen–producing empyema, and age at follow-up evaluation (12 ± 5 years). Only one child reported recurrent respiratory symptoms. No child had restrictive spirometric changes (total lung capacity, <80%; vital capacity, <80% predicted) but seven of 15 had a reduced forced expiratory volume in 1 second (<80% predicted) or forced expiratory flow during the middle half of the vital capacity (<75% predicted), suggesting mild airway obstruction. No child demonstrated reduced exercise tolerance due to restrictive ventilatory limitations. Mild obstructive abnormalities in lung function were identified with equal frequency in children treated with and without chest tube drainage.

(*AJDC.* 1990;144:1337-1342)

Continuous closed chest tube drainage and concomitant parenteral antibiotic therapy have been the standard treatment of empyema in children since the early 1970s.[1-3] Short-term benefits attributed to the thorough drainage of the empyema include reduced mortality[4-6] and shorter durations of toxicity,[6,7] fever,[7,8] and hospitalization.[5,6,9] Chest tube drainage in adults may also reduce the likelihood of long-term fibrothorax and restrictive lung disease.[7] The influence of chest tube therapy on the long-term outcome in children recovering from empyema is less clear. Recent reports suggest that chest tubes may not be necessary to achieve complete clinical recovery in children with empyema if appropriate antibiotic therapy and supportive care are provided.[8,10,11] Murphy et al[8] described three children with pneumococcal empyema who clinically recovered without evidence of residual restrictive lung disease when treated with thoracentesis and antibiotics alone.[8] Other investigators have observed that roentgenographic evidence of pleural disease often completely resolves regardless of whether chest tubes are used to treat children with empyema.[11-13]

Spirometry at rest and measurement of cardiopulmonary response to exercise were used in 15 children aged 2 to 11 years following empyema to better describe the long-term outcome of these patients. The children were grouped according to whether they received chest tube drainage to determine whether those treated with antibiotics and thoracentesis have a comparable incidence of restrictive lung disease and/or abnormal cardiopulmonary response to exercise compared with patients treated with antibiotics and pleural drainage with chest tubes.

PATIENTS AND METHODS

Between January 1976 and December 1986, 57 children were admitted to Children's Hospital and Medical Center, Seattle, Wash, with a diagnosis of empyema based on the presence of a purulent pleural exudate, pleural involvement seen on roentgenograms, and one of the following: a positive bacterial culture of pleural fluid or a negative pleural culture associated with a positive blood culture, a positive latex agglutination test, or a positive countercurrent immune electrophoresis for a known bacterial pathogen. Twenty-six subjects were selected for follow-up study based on the following criteria: (1) younger than 18 years at the time of acute illness, (2) appropriate antibiotic therapy administered based on findings of cultures and antibiotic sensitivity profiles, (3) recovery interval from initial infection greater than 2 years, and (4) present age of 6 years or older to perform effort-dependent pulmonary function and exercise stress tests.

Children who required chest tube placement because of imminent respiratory failure (based on a respiratory rate of >60 breaths per minute, inspired oxygen supplementation of >0.50 fraction of inspired oxygen or >2 L/min, or arterial P_{CO_2} >50 mm Hg) were excluded to make the groups more comparable with respect to severity of the empyema at the time of hospital admission. Only one patient was excluded for this reason. Also excluded were four patients who developed empyema following thoracic surgery. Before patient contact, the study protocol was reviewed and approved by the Human Subjects Committee of the hospital. Fifteen of the remaining 21 subjects agreed to travel to Children's Hospital and Medical Center for follow-up pulmonary evaluation. The laboratory methods by which empyema was diagnosed in each enrolled patient are presented in Table 1. All children and/or their parents gave written consent for enrollment before study. Seven children who had undergone chest tube drainage at the onset of hospitalization and received parenteral antibiotics were designated as group 1. Group 2 included eight children who had received only parenteral antibiotics.

The medical records of both groups were reviewed for age at time of empyema, sex, causative organism, duration of hospitalization and administration of parenteral antibiotics, and duration of temperature greater than 38.5°C following initiation of antibiotic treatment. The decision to use chest tube drainage as a part of therapy was dictated by the clincial assessment and biases of the vari-

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From the Department of Pediatrics, University of Washington School of Medicine and Children's Hospital and Medical Center, Seattle.

Reprint requests to Division of Neonatal and Respiratory Diseases, Department of Pediatrics, Mail Stop RD-20, University of Washington School of Medicine, Seattle, WA 98195 (Dr Redding).

Table 1.—Features of Pleural Fluid in Children With Empyema*

Patient No.	Culture	CIE	Gram's Stain	WBC Count, $\times 10^9$/L	PMN
Group 1					
1	−	+	. . .	7	0.83
2	−	+	+	. . .	. . .
3	+	. . .	−	57	0.59
4	+	. . .	+	. . .	. . .
5	+	+	+	171	0.98
6	+	+	+	39	0.77
7	−	+	+	254	1.00
Group 2					
8	−	+	+	44	0.99
9	+	+	+	108	1.00
10	+	+	+	33	. . .
11	−	+	+	9	0.96
12	−	+	+	14	0.85
13	+	+	+	12	0.95
14	+	+	. . .	. . .	. . .
15	−	+	+	40	0.43

*CIE indicates counterimmune electrophoresis for *Haemophilus influenzae* or *Streptococcus pneumoniae*; WBC, white blood cell; PMN, polymorphonuclear leukocytes; plus sign, positive; and minus sign, negative.

Table 2.—Clinical Characteristics of Study Group at the Time of Empyema*

Variable	Group 1	Group 2
No. of patients	7	8
Sex, M:F	3:4	2:6
Age at time of empyema, y	6.8 ± 4.2	5.9 ± 4.5
No. of thoracenteses	9	11
Organism		
Streptococcus pneumoniae	3	7
Haemophilus influenzae	2	2
Staphylococcus aureus	1	0
Fusobacterium nucleatum	1	0
Roentgenographic pleural thickness (n = 9)		
Millimeters	12 ± 5	20 ± 5
% Chest width	20 ± 13	21 ± 4
HR at chest tube placement or day 3 of hospitalization	130 ± 26	120 ± 17
RR at chest tube placement or day 3 of hospitalization	32 ± 10	38 ± 11
Temp$_{max}$ at chest tube placement or day 3 of hospitalization	38.5 ± 0.9	38.9 ± 1.0
Hospitalization, d†	17 ± 3	12 ± 3
Fever after onset of parenteral antibiotics, d	6 ± 4	7 ± 5
Parenteral antibiotics, d†	17 ± 4	10 ± 4
Duration of chest tube in 6 of 7 patients, d	5 ± 1	. . .

*Values are mean ± SD unless otherwise stated. HR indicates heart rate; RR, respiratory rate; and Temp$_{max}$, maximum temperature.

†Significant difference ($P < .05$) between groups 1 and 2.

ous attending physicians who managed this group of patients. Specific rationales for pleural drainage procedures were not well documented. Therefore, to determine retrospectively whether one group was more severely ill than the other, average heart rate and respiratory rates as well as the maximum temperature on the day of chest tube placement in group 1 were compared with the same indexes recorded for group 2 patients on the third hospital day (the average day of hospitalization when chest tubes were placed in group 1 patients). In addition, the thickness of pleural fluid at the fifth rib on the chest roentgenogram obtained with the patient in the lateral decubitus position at the time of admission was measured in millimeters and as a percent of chest width to compensate for children of different sizes.

Follow-up pulmonary function testing occurred when patients had been free of respiratory infection for at least 6 weeks. Before testing, each subject or parent reported from recall the number of lower respiratory tract infections per year that required visits to the physician's office or hospitalization subsequent to the empyema.

Each subject underwent spirometry at rest with use of a body plethysmograph (Gould Medical Corp, Dayton, Ohio, or Medical Graphics Corp, St Paul, Minn). Vital capacity and forced expiratory flow during the middle half of vital capacity (FEF$_{25\%-75\%}$) were expressed as a percentage of predicted norms.[14] Forced expiratory volume in 1 second (FEV$_1$) was expressed as both a percentage of predicted and as a percentage of vital capacity (FEV$_1$%VC). Body plethysmography was also used to measure absolute lung volumes, including total lung capacity (TLC), residual volume, residual volume–to-TLC ratio, and functional residual capacity. These values, except for the residual volume–to-TLC ratio, were also expressed as percentages of published norms.[14] All TLC values less than 80% predicted were considered evidence of restrictive lung disease. Values of FEV$_1$%VC less than 80% and/or FEF$_{25-75\%}$ less than 75% predicted were considered evidence of airway obstruction.

The patients then rode an exercise bicycle ergometer (Quinton, Seattle, Wash) according to the James et al[15] protocol for children. Cardiopulmonary indexes were measured with a heart rate monitor (Hewlett Packard, Waltham, Mass), exhaled gas concentrations with use of oxygen gas and carbon dioxide analyzers (Beckman OM-11 and Beckman LB2, respectively, Beckman Corp, Anaheim, Calif), and a pneumotachygraph (Hewlett-Packard No. 2). Analog signals were digitized, averaged, and stored on a personal computer every 20 seconds. Indices used to evaluate cardiopulmonary response to exercise included maximal tidal volume (Vt$_{max}$) and respiratory rate, minute ventilation, maximal heart rate, and maximum oxygen consumption ($\dot{V}O_2$ max) during the last 30 seconds of each 2-minute interval of measured work loads. Only indices measured during the greatest work load are presented and compared between the two groups. Maximum voluntary ventilation (MVV) was calculated as FEV$_1$ times 35.[16] Heart rate and $\dot{V}O_2$ were expressed as a percentage of the predicted value with use of age- and weight-specific norms.[16]

Two measurements were used to identify exercise limits specifically due to ventilation limitation. The first was loss of breathing reserve, defined as 1.0 minus the ratio of maximum exercise ventilation (MEV) to the MVV or 1 − MEV/MVV. Normal subjects taller than 120 cm are not ordinarily limited by ventilation and have a breathing reserve of at least 40% during maximum exercise.[17] A reserve of less than 20% or, conversely, an MEV/MVV ratio greater than 80% identifies patients likely to be limited by ventilation at maximum exercise. Breathing reserve can be reduced in patients with either restrictive or obstructive lung disease.[18] One group 1 patient and two group 2 patients were less

Table 3.—Resting Spirometric Values and Exercise Response in Children Who Have Recovered From Empyema*

Variable	Mean ± SD (Range)
FVC, % predicted	
Group 1	100 ± 16 (85-138)
Group 2	93 ± 9 (75-107)
FEV$_1$, % predicted	
Group 1	80 ± 13 (59-94)
Group 2	83 ± 12 (58-96)
FEV$_1$/FVC, %	
Group 1	77 ± 10 (62-92)
Group 2	80 ± 6 (68-90)
FEF$_{25\%-75\%}$, % predicted	
Group 1	69 ± 17 (42-101)
Group 2	85 ± 19 (56-110)
TLC, % predicted†	
Group 1	103 ± 14 (83-119)
Group 2	99 ± 15 (82-130)
RV, % predicted†	
Group 1	134 ± 62 (44-214)
Group 2	131 ± 57 (63-252)
RV/TLC, %†	
Group 1	29 ± 12 (7-42)
Group 2	34 ± 6 (24-40)
FRC, % predicted†	
Group 1	111 ± 18 (84-137)
Group 2	112 ± 22 (95-164)
MEV/MVV	
Group 1	75 ± 16 (58-104)
Group 2	74 ± 18 (58-107)
HR$_{max}$, %	
Group 1	96 ± 7 (83-104)
Group 2	93 ± 8 (79-107)
RR$_{max}$	
Group 1	44 ± 5 (34-49)
Group 2	47 ± 6 (35-57)
Vt$_{max}$/IC	
Group 1	0.7 ± 0.2 (0.5-1.0)
Group 2	0.7 ± 0.1 (0.5-0.8)
$\dot{V}O_2$max, %	
Group 1	64 ± 21 (30-99)
Group 2	75 ± 14 (44-95)

*Values for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV$_1$), forced expiratory flow during the middle half of vital capacity (FEF$_{25\%-75\%}$), total lung capacity (TLC), residual volume (RV), and functional residual capacity (FRC) are expressed as the percent of normal based on previously published norms. MEV/MVV indicates the ratio of maximum exercise ventilation to the maximum voluntary ventilation; HR$_{max}$, maximum heart rate; RR$_{max}$, maximum respiratory rate; Vt$_{max}$/IC, ratio of tidal volume at maximum exercise to resting inspiratory capacity; and $\dot{V}O_2$max, maximum oxygen consumption.

†Data are from 13 patients, six form group 1 and seven from group 2.

than 120 cm tall. We interpreted the completion of maximum predicted exercise by these three children as evidence that they were not ventilation limited. The second discriminating variable was the ratio of Vt$_{max}$ at maximum exercise to resting inspiratory capacity (IC) or Vt$_{max}$/IC. A value of 1 or more in conjunction with a respiratory rate of more than 50 breaths per minute at maximum work rate reflects specifically restrictive lung disease as a contributing factor in exercise limitation.[17]

Those who administered the tests were "blinded" to each child's initial therapy, as were those who interpreted the spirometric and exercise data.

DATA ANALYSIS

Comparisons between the groups were made with use of unpaired *t* tests and, where appropriate, nonparametric methods with the Mann-Whitney *U* test (SPSS-PC Plus, Microsoft, Bellevue, Wash [1986]). $P<.05$ was considered significant.

RESULTS

Short-term Response to Therapy

The characteristics of both groups of children at the time of admission and during their hospital course are summarized in Table 2. The average ages at onset of empyema and the sex distribution of children in groups 1 and 2 were similar. All subjects developed empyema as older children, but this occurred predominantly in female subjects in both groups. *Streptococcus pneumoniae* or *Haemophilus influenzae* caused empyema in most children in both groups. The chest roentgenograms revealed statistically similar pleural fluid thickening in group 2 compared with group 1 when measurements were expressed in millimeters or as a percentage of thoracic width. This comparison excluded one child in group 1 and two children in group 2 with complete opacification of the involved side and absence of pleural layering. Chest tube placement occurred as mean (±SD) of 3±2 days after hospitalization in group 1 patients. Six patients had a single chest tube placed and one had three chest tubes placed. Six of eight patients in group 2 underwent one thoracentesis; three patients underwent two thoracenteses. The volume of pleural fluid extracted by initial thoracentesis varied from 12 to 1100 mL in group 1 and from 10 to 325 mL in group 2. No statistically significant differences were observed between the groups with respect to heart rate, respiratory rate, or maximum temperature on the day of chest tube placement compared with the third day of hospitalization in those treated without chest tube placement (Table 2).

The mean duration of drainage in six of the seven group 1 patients was 4.7 days (range, 3 to 7 days). Mean pleural drainage from these six children was 370±260 mL following the initial thoracentesis. The seventh patient was hospitalized twice for the treatment of the same pneumococcal empyema. Chest tube drainage was performed for 3 days of the initial 15-day hospitalization. Pleural fluid reaccumulated 1 week after discharge, and she was readmitted for 13 days when two chest tubes were placed and allowed to remain, cut off flush with skin, for several months.

Patients treated with chest tube drainage were hospitalized and received parenteral antibiotic therapy for a longer time compared with those treated with antibiotics alone (Table 2). The duration of fever from the onset of antibiotic therapy was no different between the two groups.

Long-term Response to Therapy

The mean age at follow-up testing was similar for both groups (12±4 years in group 1 and 13±7 years in group 2), as was the mean interval from empyema to follow-up evaluation (5±3 years for group 1 and 6±3 years for group 2, respectively). No child was hospitalized

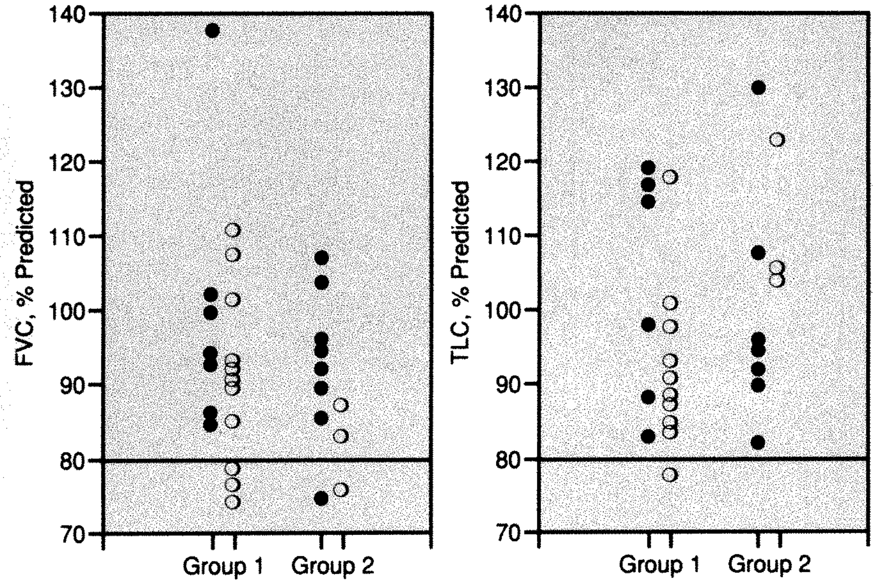

Fig 1.—Individual spirometric values are expressed as percents of the predicted norms for forced vital capacity (FVC) and total lung capacity (TLC). Thirteen of the 15 children were able to perform pulmonary functions with use of the body plethysmograph; all 15 performed spirometric testing without difficulty. Closed circles indicate data from the current study; open circles, data from Murphy et al[8] and McLaughlin et al[19] in children who recovered from empyema. Group 1 patients underwent chest tube drainage; group 2 patients did not. Lines at 80% predicted VC and TLC represent lower limits of normal values.

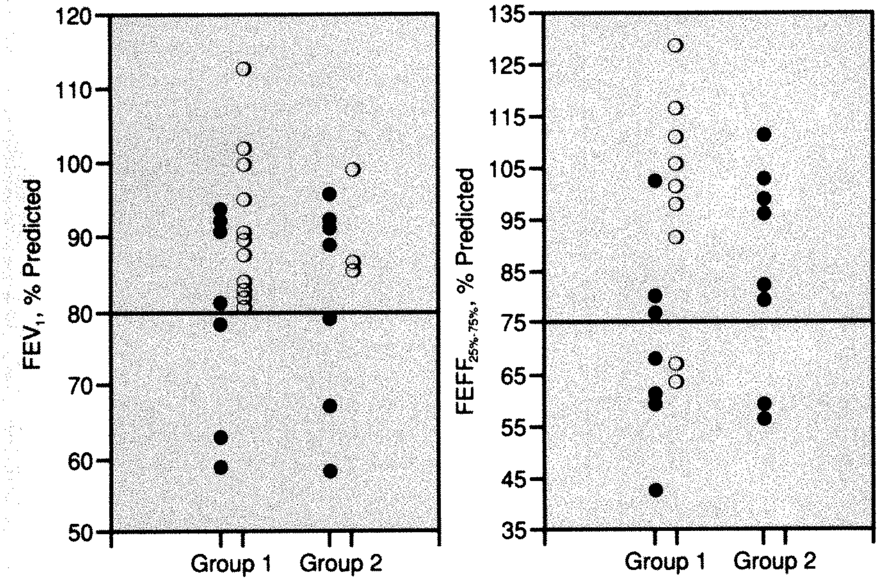

Fig 2.—Individual spirometric values are expressed as percents of predicted norms for forced expiratory volume at 1 second (FEV$_1$) and forced expiratory flow during the middle half of vital capacity (FEF$_{25\%-75\%}$). Closed circles indicate data from the current study; open circles, data from Murphy et al[8] and McLaughlin et al[19] in children who recovered from empyema. Group 1 patients underwent chest tube drainage; group 2 patients did not. Lines at 80% for FEV$_1$ and 75% for FEF$_{25\%-75\%}$ represent lower limits of normal values. Two patients in group 2 had FEV$_1$ values that were 91% of predicted values; their data points are superimposed on one another.

subsequent to the empyema for respiratory problems. Only one child (group 1) reported a recurrence of lower respiratory tract symptoms that required medical attention following clinical resolution of the empyema.

There were no statistical differences in group mean values for any spirometric index at rest (Table 3). Individual values within each group for TLC, forced vital capacity, FEV$_1$, and FEF$_{25\%-75\%}$ are portrayed as solid points in Figs 1 and 2. Four of seven group 1 patients and three of eight group 2 patients exhibited evidence of mild obstructive disease, defined as an FEV$_1$ value 80% or less than the predicted value and/or an FEF$_{25\%-75\%}$ less than 75% of predicted value. Correcting FEV$_1$ for vital capacity (FEV$_1$%VC) did not change the number of children identified as having mild airway obstruction. One of these patients from group 1 had a history of asthma before the empyema. None of the 13 patients tested by body plethysmography had restrictive lung disease based on a reduced TLC and vital capacity. The one patient (group 2) with a vital capacity 75% of the predicted value had a TLC 92% of the predicted value and an FEV$_1$ 58% of the predicted value, suggesting obstructive more than restrictive disease.

The indexes used to compare the cardiopulmonary responses to exercise are presented in Table 3 and Fig 3. There were no significant differences between the groups in the mean values of any index. Mean heart rate at maximal exercise, expressed as percentage of predicted value at maximum work load, was normal and similar in both groups (Table 3), suggesting that all children performed to their maximum ability.

The results for MEV/MVV, which reflects breathing reserve, listed in Table 2 and depicted in Fig 3, do not include the three children less than 120 cm tall who are not expected to have a reserve. Two of six group 1 patients and two of seven group 2 patients had MEV/MVV ratios greater than 80%, suggesting reduced breathing reserve during exercise. One of these group 1 patients and one patient in group 2 had spirometric evidence of airway obstruction to explain their reduced breathing reserve. The other two patients had MEV/MVV ratios of 84% (group 1) and 81% (group 2) but normal spirometric values. They were both well-conditioned 16-year-old boys who performed maximal predicted exercise. Each was limited during exercise by heart rate; neither breathed faster than 50 breaths per minute during maximum exercise. Only one subject (group 1) had a Vt$_{max}$/IC ratio of 1, but he did not breathe faster than 50 breaths per minute. Three subjects from group 2 breathed faster than 50 breaths per minute, but none achieved

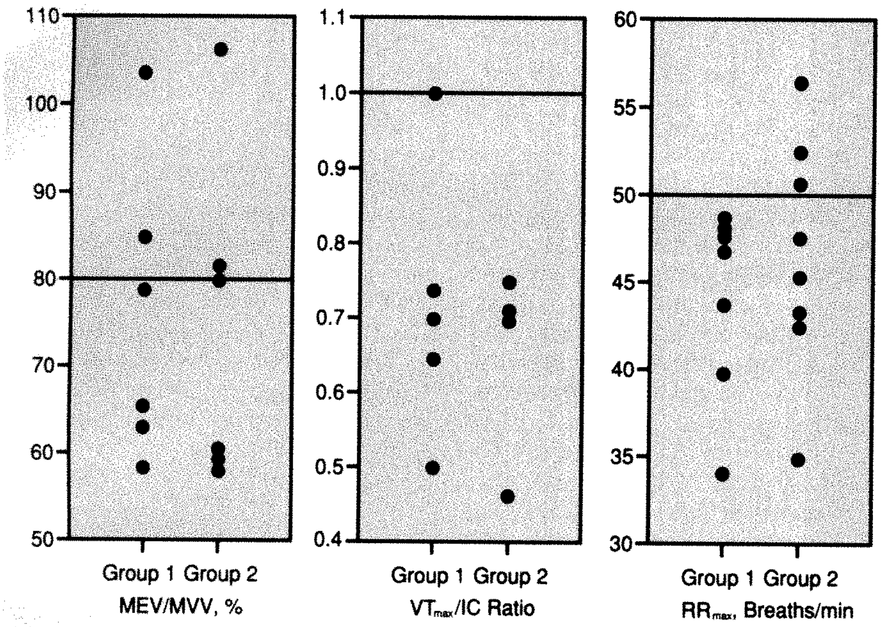

Fig 3.—Individual data from patients in group 1 (who underwent chest tube drainage) and group 2 (who did not undergo chest tube drainage) during exercise. Three children (one in group 1 and two in group 2) were less than 120 cm tall and were consequently excluded from determinations of the ratio of maximum exercise ventilation to maximum voluntary ventilation (MEV/MVV). Use of greater than 80% MEV/MVV ratios reflects abnormal use of breathing reserve during exercise. The ratios of maximal tidal volume to inspiratory capacity (Vt_{max}/IC) greater than 1.0 in conjunction with respiratory rates greater than 50/min denote patients with exercise limitation due to restrictive lung disease. RR_{max} indicates maximum respiratory rate.

Vt_{max}/IC ratios of 1 or more. These results suggest that no child had exercise limitation due to restrictive lung disease.

Neither group achieved predicted $\dot{V}O_2$max values during exercise despite achieving maximal predicted heart rates (Table 3). These results suggest that most subjects were deconditioned but were not limited by ventilation.[16]

COMMENT

The spirometry results from this study extend observations made by Murphy et al[8] and McLaughlin et al[19] involving long-term outcome of lung function in children treated for empyema. The results of these two studies are portrayed in Figs 1 and 2 as open circles along with our results to further describe lung function an average of 6 years after empyema. These data depict a similar scattering of individual values among children who were treated with chest tube drainage and those who were not. The majority of patients in both groups showed no evidence of restrictive lung disease based on a TLC value less than 80% of the predicted value. In contrast, seven of the 15 children examined in our study had evidence of mild obstructive changes. Airway obstruction was not reported by McLaughlin et al. Murphy et al did not describe reduced FEV_1 values but did report that the residual volume–to-TLC ratio was increased in four of their five cases in the presence of normal TLC values, suggesting air trapping due to small-airway obstruction. "Obstructive bronchitis" has also been noted by Hartl[9] in eight of 14 children who underwent chest tube drainage after 3 days of hospital treatment for empyema in infancy; however, the report did not contain individual values for direct comparison.

The frequency of obstructive changes in our study was similar in subjects who underwent chest tube therapy and those who did not, suggesting that this sequela may relate to the original pleuropulmonary infection rather than to the therapy provided. Airway obstruction and airway hyperreactivity have been reported in patients who have recovered from croup, bronchiolitis, and hydrocarbon aspiration.[20] It is conceivable that bacterial pneumonia and empyema represent another form of airway injury leading to subsequent airway scarring and persistent obstruction in growing children. Airway reactivity in children who have recovered from empyema has not been investigated.

Among studies that have addressed the long-term outcome of children with empyema since 1965, the most consistent findings have been complete clinical recovery with no residual symptoms,[11,12,19,21,22] complete return of chest roentgenograms to normal,[11,13,23] and no exercise intolerance by history.[8,23] Our findings extend the latter clinical impressions, as all 15 children showed no ventilation limitation during exercise due to restrictive lung disease and only four children exhibited mild limitation with spirometric evidence of obstructive lung disease. However, most children acheived less-than-normal oxygen consumption at a time when heart rates were maximal, suggesting that children in both groups were deconditioned.

The conclusion that chest tube placement may not be necessary to achieve optimal long-term outcome of children with empyema contains several caveats. All children studied were older and well past infancy when the empyema occurred, thereby representing a low-risk group for mortality associated with empyema.[2] In addition, most of the children experienced infection due to *S pneumoniae* or *H influenzae* type b and not *Staphylococcus aureus*. Empyema associated with *S aureus* accounts for most of the mortality associated with empyema in infants and children.[2,5,6] Our subjects were therefore at lower risk for immediate complications, thereby allowing clinicians to withhold immediate chest tube drainage as a necessary part of therapy.

Pleural fluid was not routinely cultured for anaerobic bacteria in our study patients. These organisms are detected alone or mixed with aerobic organisms in the pleural fluid of most adults with empyema.[24] The absence of pleural anaerobic organisms in many children with empyema may in part account for the improved roentgenographic and spirometric outcomes of children compared with adults following empyema. Among children with empyema caused by anaerobic organisms, a significant number have undergone not only chest tube drainage but also decortication.[25] The short- and long-term outcomes of children with pleural disease caused by anaerobic organisms and their requirement for chest tube drainage will require prospective evaluation for anaerobic organisms.

A major presumption made in this retrospective study is that the children had pleural infections of comparable severity. A variety of objective indexes listed in Table 2 were retrieved by chart review so that the reader can conclude whether the two groups were similar or different. Children presenting with respiratory failure presumably were sicker and required immediate pleural drainage; these patients were excluded from our study. Among the subjects studied, the vital signs by the third hospital day, the day on which most children underwent chest tube placement, were similar in both groups, as was the thickness of pleural fluid as seen on chest roentgenograms obtained at the time of admission. Duration of fever after initiation of antibiotic therapy was also similar for the two groups. These retrospective findings do not explain why some children underwent chest tube drainage and others did not. The decision to perform chest tube drainage was made by several attending physicians based on rationales and biases that were not consistently recorded in the hospital charts. The longer hospitalization and duration of parenteral antibiotic treatment in the group undergoing chest tube placement may reflect more severe pulmonary disease due to empyema or alternatively reflect reduced mobility and increased chest wall pain due to the chest tube itself.

In summary, the vast majority of older children with empyema recover without persistent or recurrent respiratory symptoms. Their lung function tests show evidence of mild airway obstruction as well as some increased use of ventilatory reserve during exercise in a minority of patients regardless of whether they underwent chest tube drainage. Long-term restrictive lung disease—as measured by spirometry, body plethysmography, and exercise testing—is rare in children several years after clinical recovery from empyema. Closed chest tube therapy is not mandatory to ensure the long-term pulmonary recovery of otherwise normal older children with empyema produced by *S pneumoniae* or *H influenzae*; however, it remains an important option in the treatment of patients with rapidly developing or severe pleural infection and of children with empyema who exhibit slow improvement during the course of parenteral antibiotic treatment.

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Newborn Screening for Sickle Cell Disease

When Is an Infant 'Lost to Follow-up'?

Scott T. Miller, MD; Tziporah V. Stilerman, PA; Sreedhar P. Rao, MD; Sunil Abhyankar, MD; Audrey K. Brown, MD

• Success of programs to screen newborns for sickle cell disease depends on timely follow-up. Education regarding fever and splenic palpation, and initiation of prophylactic penicillin therapy, will reduce morbidity and mortality and should occur prior to 4 months of age. However, contacting parents to permit implementation of care may be difficult, particularly in large urban populations; only nine (36%) of 25 infants recently identified as having sickle cell disease arrived at our institution for initial appointments. Medical providers must be aware of medical and legal obligations related to follow-up of newborns with sickle cell disease to prevent untoward events in "missed cases."

(*AJDC.* 1990;144:1343-1345)

Screening of newborns for sickle cell disease and other hemoglobinopathies is now performed in 22 states and in the District of Columbia.[1] For these programs to be successful, parents of affected infants must be notified promptly so that appropriate counseling, education, and initiation of pneumococcal prophylaxis with penicillin can occur, preferably by 4 months of age.[2] Potential pitfalls in this crucial notification and retrieval process have not been explored, and they provide the basis for this report.

METHODS

Infants born at Kings County Hospital Center or University Hospital of Brooklyn (NY) between June 1, 1988, and January 1, 1989, and identified by newborn screening as having sickle cell disease, form the basis of this report; all were at least 5 months of age at the time of this writing.

All newborns in New York State are screened for hemoglobinopathies at a central laboratory using a heel-stick filter paper blood specimen.[3] The screening laboratory recognizes our institution as a regional Blood Dyscrasia Center for the New York State Department of Health. If a newborn is suspected to have a form of sickle cell disease, the screening laboratory telephones the coordinator (T.V.S.) of our Infant Sickle Cell Clinic and provides the name, medical record number, date of birth, address, and, if available, telephone number of the patient and his or her guardian, usually within 2 weeks after birth. Letters are also sent from the laboratory to the hospital and physician of record.

If parents can be reached by telephone, they are informed that a test for sickle cell disease is routinely administered to all newborns, that their child's test result was suggestive of the disease, and that confirmatory testing is necessary. An appointment is made for the next Infant Sickle Cell Clinic, which meets weekly and provides "well-baby" as well as comprehensive sickle cell care to children under 4 years of age. Similar information and an appointment date are sent by first-class mail if parents cannot be reached by telephone.

The following methods are used to reach those parents who do not appear for scheduled appointments: (1) certified mail is sent to all nonresponders; (2) the *Address Telephone Directory* (updated every 13 weeks by our local telephone company and currently available at a cost of $114), which is indexed by customer addresses and enables correction of telephone numbers or calls to neighbors of parents who had nonworking numbers listed on charts, is used; (3) a standard telephone directory is used to call all potential relatives of an affected infant with an unusual last name; (4) birth certificate office records sometimes provide an alternative address.

Parents who express a preference for pediatric care elsewhere are asked to provide the physician's name and telephone number. The physician is then contacted and alerted to the suspected diagnosis and the need for confirmatory testing; the physician's willingness and ability to provide care for infants with sickle cell disease is also ascertained.

RESULTS

Twenty-five infants with sickle cell disease identified by screening were born at our institution during a 7-month period from June 1, 1988, through January 1, 1989. Fourteen newborns showed an FS pattern on electrophoresis (fetal and sickle hemoglobin only, compatible with homozygous sickle cell disease or sickle β^0-thalassemia), nine had FSC (sickle hemoglobin C disease), and two had FSA (sickle β^+-thalassemia).

Attempts were made to contact the infants' parents as outlined above. Only nine patients arrived for their initially scheduled visits. The various problems resulting in failure of the remaining 16 infants to arrive in the clinic are listed in the Table. One mother, who failed to respond to two letters, arrived in the clinic only after a certified letter had been sent; she complained that mail theft was a major problem in her building and she had not received the two previous letters. A brief delay in one infant's arrival was due to misunderstanding or miscommunication of the patient's address during the initial telephone call from the screening laboratory; this was apparent when notification of the abnormal results from the hemoglobin screening arrived by mail. The birth certificate office provided a correct address, different from that obtained from the medical record, for one infant; this sometimes occurs if parents are illegal immigrants. The delinquent mother of one infant had sickle hemoglobin C disease. Although she had had several clinical problems related to sick-

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From the Department of Pediatrics, State University of New York–Children's Medical Center of Brooklyn.

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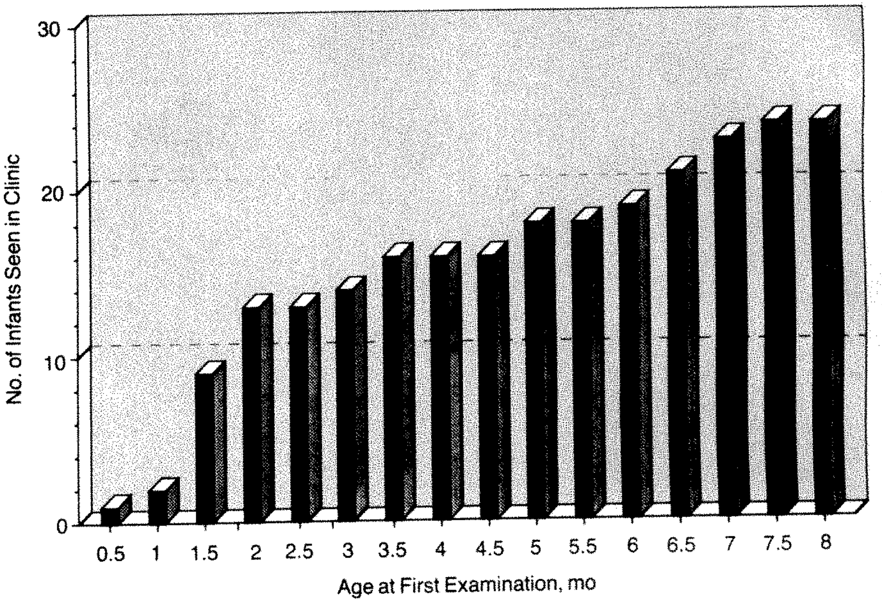
Reasons for Missed First Appointment

Reasons	No. of Patients (N=16/25)
Children in foster care	3 (1 twin pair)
Language difficulties	3 (1 twin pair)
Mail theft	1
Address problems	
Wrong on phone call, right on letter from screening laboratory	1
Birth certificate address different but correct	1
Incorrect address on chart and birth certificate	3
Scheduling problems, denial, other	4



Cumulative number of infants with sickle cell disease seen by a physician. Thirteen of 25 infants were seen by 2 months of age; one has not yet been contacted after 7.5 months of age.

ling complications of her own disorder, she did not feel compelled to come to a clinic to confirm the diagnosis in the child.

The Figure depicts on the ordinate the number of infants with sickle cell disease identified by screening of newborns vs the interval between birth and arrival at our clinic. Sixty-four percent of infants were seen by 4 months of age, and only one (4%) remained delinquent at more than 7 months of age. Three infants were contacted when two (including one of a twin pair) were hospitalized at 2 months and at 3.5 months of age for gastroenteritis. All infants contacted to date have been seen prior to experiencing clinical complications of their disease.

COMMENT

Mass screening of newborns for hemoglobinopathies must be coupled with comprehensive follow-up programs if the goals of diminished morbidity and mortality are to be realized.[4-7] Recognition that pneumococcal sepsis may occur as early as 4 months of age[8] and that its incidence and mortality may be reduced by a prophylactic regimen of penicillin,[2] mandates early retrieval and education of parents of newborns with sickle cell disease. Mortality due to acute splenic sequestration, another life-threatening complication of sickle cell disease during infancy, may also be reduced by early intervention.[9]

It is thus clear that follow-up of newborns with sickle cell disease must be not only complete, but timely. An early report of a successful follow-up program for infants in New York City was criticized for failing to retrieve 10 newborns (7% of those identified by screening) to appropriate medical care.[10] While the authors responded that three additional infants subsequently appeared for ongoing medical care, timeliness of this appearance for medical care is not stated for either the original cohort or the three delinquent infants. Similarly, in a recent report of successful reduction of infant mortality related to screening of newborns in California,[7] eight (9%) of 89 infants with abnormal screening results (two with hemoglobin SC and six with homozygous [SS] sickle cell disease) were "lost to follow-up." Attempts made at retrieval are not stated, and the age at which the remaining 81 infants were seen in a clinic is not mentioned. Investigators from North Carolina have recently reported a reduction in median time to the first clinic visit from 61 to 24 days, as health care personnel became more familiar with follow-up problems.[11] Because our retrieval problems exist despite a focused attempt to locate patients, it is uncertain whether the median follow-up time of 2 months for our own newborn cohort can be significantly improved. We do hope that the percentage of infants seen by 4 months of age (64% in this series) can be appreciably increased.

Problems related to the follow-up of infants with abnormal newborn screening results are discussed by investigators at the Centers for Disease Control, Atlanta, Ga,[12] in an analysis of missed cases of phenylketonuria and congenital hypothyroidism. Despite the fact that data were obtained by canvassing newborn-screening laboratory directors, who are not necessarily informed of missed cases due to follow-up problems, 16% of 76 missed cases were attributed to problems in follow-up. It is noteworthy that the specific events listed as causes of unavailability for follow-up in the study (five patients were "transferred to care of another physician," four "moved," and one was "hard to locate") are similar to our own problems listed in the Table; all might well have been correctable by a more concerted follow-up effort. It is also noteworthy that at least 29% of missed cases of phenylketonuria and hypothyroidism resulted in litigation; the legal status of an additional 25% was unknown. It seems likely that medicolegal considerations may in fact ultimately provide additional impetus for expanded support of hemoglobinopathy follow-up programs.

The proven efficacy of penicillin for pneumococcal prophylaxis has unequivocally established the need for prompt retrieval of affected infants. While most state laws related to newborn screening still do not even address the follow-up phase of a screening program,[13] New York State Law was modified in 1987 to legally assign follow-up responsibility to both the hospital of birth and physician of record.[14] The law mandates not only that those responsible parties collect and submit confirmatory specimens as requested by the screening laboratory, but also "in the case of confirmed abnormal test results, arrange for diagnostic evaluation and case management with an approved specialized care center."

The need for expeditious follow-up is thus well established from both medical and legal standpoints. Our own experience demonstrates that, even with careful attention to this need, there are multiple impediments to prompt identification and retrieval of infants having sickle cell disease detected by newborn screening. This is particularly true in the inner city, where single-parent families, frequent surname changes, frequent address changes, and illegal aliens' fears of identification by legal authorities are major problems. These problems can only be overcome through persistent and often imaginative efforts of concerned health care providers. We have recently attempted to streamline our retrieval process by earlier use of certified mail and earlier involvement of child welfare agencies; however, the process remains a formidable one. We strongly recommend that all centers with a large population at risk for sickle cell disease have a designated contact person available for notification by the screening laboratory. This person must then have the necessary resources available to promptly initiate the search process, using, where necessary, the diligent detective work as described above.

We have been fortunate that our own delinquent infants, save one, have been found; none suffered a life-threatening complication of disease prior to being contacted. It is clear that physicians and hospitals must be made aware of the follow-up responsibilities associated with screening of newborns, and appropriate resources must be made available to prevent a "missed case" of sickle cell disease arriving in an emergency room dead on arrival due to pneumococcal sepsis.

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In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

Relationships Between Central and Autonomic Measures of Arousal at Age 15 Years and Criminality at Age 24 Years

Adrian Raine, DPhil; Peter H. Venables, DSc; Mark Williams, MA (*Arch Gen Psychiatry.* 1990;47:1003-1007)

Spinal Bone Mineral Density in Children Aged 5.00 Through 11.99 Years

Stephen W. Ponder, MD; David P. McCormick, MD; H. Daniel Fawcett, MD; Judy L. Palmer, PhD; Margaret G. McKernan; Ben H. Brouhard, MD

• Lumbar spine (L-2, L-3, L-4) bone mineral density was measured in 184 healthy boys and girls aged 5.00 through 11.99 years by dual photon absorptiometry. Weight, height, age, triceps skinfold thickness, and midarm circumference were also measured. Weight, height, and age were highly correlated with bone mineral density. In the population studied, a quadratic regression equation using body weight as the independent variable best described bone mineral density: bone mineral density = 0.3209 + [0.0168 (weight)] − [0.0001(weight^2)].

(*AJDC.* 1990;144:1346-1348)

Noninvasive assessment of bone mineral content (BMC) requires the use of ionizing radiation directed over a bone or group of bones.[1-3] Measurement of BMC can be performed by several methods, including standard radiography, radiogrammetry, quantitative computed tomography, neutron activation, single photon absorptiometry (SPA) and dual photon absorptiometry (DPA).[2] Except for neutron activation, all these methods measure bone mineral density (BMD), which is an indirect measure of the BMC. Quantitative computed tomography and neutron activation are precise and reliable but require exposure to ionizing radiation in the range of 200 to 5000 mrem, which makes them impractical for longitudinal studies in children.[2] Radiogrammetry and standard radiography involve the use of up to 100-mrem radiation exposure and also lack sufficient sensitivity for effective clinical use or research quantification.[2,3] Photon absorptiometry has the advantage of requiring a low radiation exposure (range, 2 to 15 mrem).[2]

The practical difference between SPA and DPA is that they measure BMD at different anatomic sites. Dual-photon absorptiometry can measure bone density in areas in which neighboring tissues are not homogeneous, such as the spine. The measurement of two photon energies (DPA) instead of one (SPA) allows for the discrimination of bone mineral from soft tissue and air interfaces.[1]

The bone architecture of the human skeleton is a combination of cortical and trabecular elements. The spine is composed primarily of trabecular bone, which is metabolically more active than cortical bone because of its greater surface area. Therefore, the spine is an ideal site for monitoring metabolic bone disease, such as osteoporosis due to glucocorticoid administration, renal disease, idiopathic osteoporosis, and axial osteomalacia.

Since the development of SPA, there have been several longitudinal and cross-sectional studies of BMC in healthy and diseased infants and children.[4-12] Sexual dimorphism in BMC has been reported in children by age 4 years.[4] Li et al[5] recently reported a higher mean BMC in black children aged 1 to 6 years than in white children. Recently, Glastre et al[11] reported data on spinal BMD in a group of 135 normal children between ages 1 and 15 years using dual energy x-ray absorptiometry. We present cross-sectionally collected data on spinal BMD in healthy children aged 5.00 through 11.99 years. The purpose of this study was to establish reference data for ongoing and future studies involving measurement of BMD in children. We hypothesized that BMD would correlate with age, weight, and height. These normative data should be useful in designing experimental protocols for the measurement of spinal BMD in children.

PATIENTS AND METHODS

Patients

Children aged 5.00 through 11.99 years were prospectively recruited from the outpatient clinics of the Child Health Center at the University of Texas Medical Branch, Galveston, and among children of employees at the university. Patient recruitment was stratified by age to ensure adequate representation in each age group for both sexes. Exclusion criteria for enrollment were the following: (1) the presence of any chronic disease, (2) a known history of metabolic bone disease, or (3) weight or height score below the fifth percentile or above the 95th percentile for age. A questionnaire was given to all parents to document the age, race, socioeconomic background, and medical history of each child. This protocol was approved by the Institutional Review Board of the University of Texas Medical Branch. Parental consent and patient assent were obtained from all participants.

Patient Data

Height was measured to the nearest 0.1 cm on a wall-mounted stadiometer by calculating the mean of three measurements. Weight in kilograms, with clothes on but without shoes, was measured on a balance scale. Trained research personnel measured all weights and heights, and all measurements were carried out on the same instruments. Mean triceps skinfold thickness in millimeters and midarm circumference in centimeters were measured on the right arm, taking the mean of three measurements.

Several parameters were derived from the physical measurements obtained from each patient. Weight and height percentiles for each child were obtained from standard growth charts.[13] Triceps skinfold percentiles were obtained from previously published reference data.[14] Percent of body fat,[15] total body fat in kilograms,[16] arm muscle area in square centimeters,[17] and body mass index[18] were also calculated. Lean body mass in kilograms was calculated by subtracting total body fat from body weight. Ratios of weight to height and weight squared to height squared were compared with the body mass index (weight divided by the square of

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From the Divisions of Endocrinology and Diabetes (Dr Ponder) and Ambulatory Pediatrics (Dr McCormick and Ms McKernan), the Department of Pediatrics; the Department of Radiology (Dr Fawcett); and the Office of Academic Computing and Biostatistics (Dr Palmer), University of Texas Medical Branch, Galveston; and the Department of Pediatrics, The Cleveland (Ohio) Clinic Foundation (Dr Brouhard).

Presented at the Society for Bone and Mineral Research Meeting, September 9-14, 1989, Montreal, Canada.

Reprint requests to the Division of Pediatric Endocrinology, Route C-63, University of Texas Medical Branch, Galveston, TX 77550 (Dr Ponder).

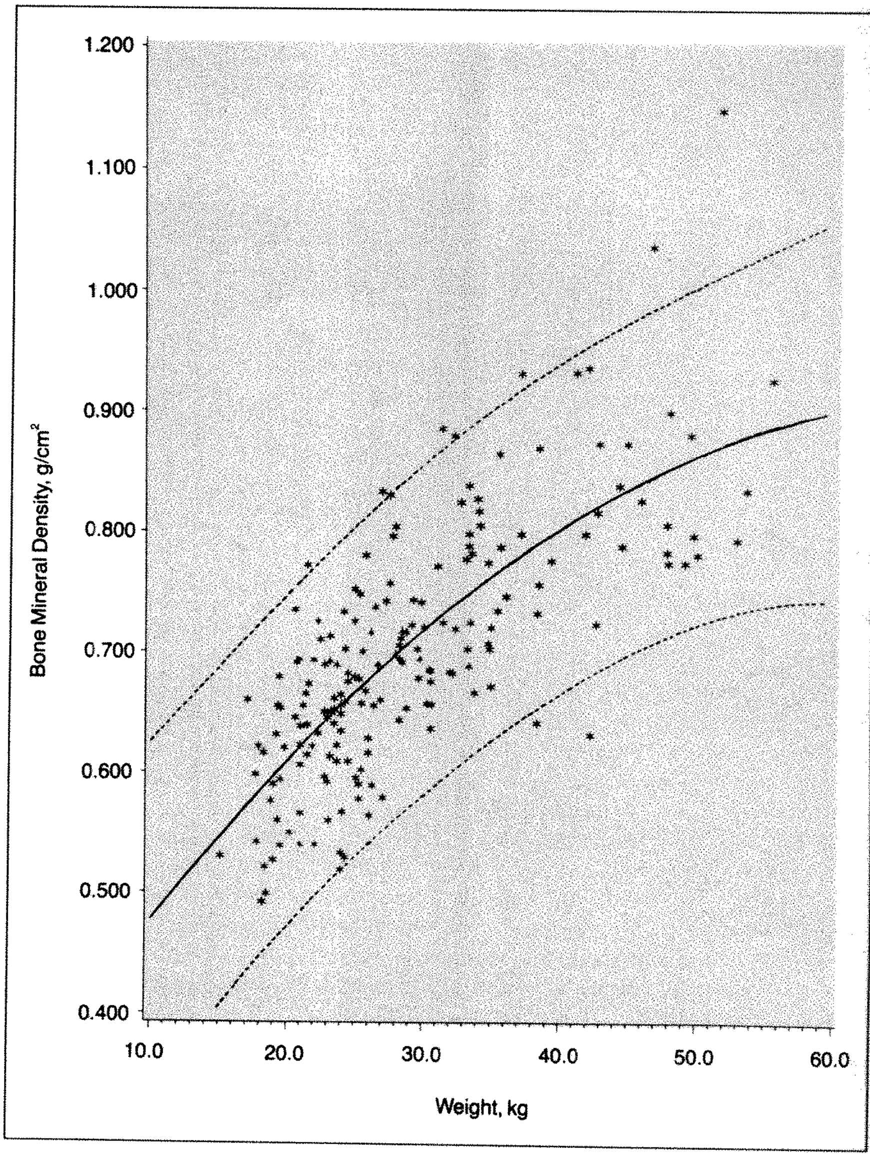
height) to define other ratios that correlated well with BMD.

Lumbar Spine Measurements

Bone mineral densitometry of the lumbar spine was performed with a dual photon absorptiometer (Lunar DP-3, Lunar Inc, Madison, Wis), which uses a gadolinium 153 source. The densitometer was calibrated daily using a phantom standard. The examination was performed with the child supine, knees flexed, and calves resting on a cushion. These maneuvers separated the spinous processes and prevented overlap of bony structures. All clothing that could produce artifacts (eg, zippers and buttons) was removed. No sedation or restraints were used. The scan time was approximately 15 minutes. The total radiation dose per scan was between 6 and 9 mrem. All scans were analyzed with the assistance of an edge detection program in the scanner software. Observer adjustment of the vertebral body locations using the edge detection software was found to be necessary much more often in child than adult spinal density measurements. To minimize this source of variability, only one experienced observer (H.D.F.) performed all scan analyses. The coefficient of variation (CV) on repeated scan analyses was 0.7%. The L-2, L-3, and L-4 spinal BMD was expressed in grams per square centimeter.

Statistical Analysis

All statistical analyses were performed using SAS statistical analysis software.[19] The median and range BMD were calculated for each age. Correlation coefficients were calculated for each variable against BMD using Spearman's rank order statistic. Single and multiple regression analyses were performed using BMD as the dependent variable and combinations of the outcome measures as independent variables.



Vertebral bone mineral density (L2-4) vs weight in 184 healthy children aged 5.00 to 11.99 years. Bone mineral density = 0.3209 + [0.0168(weight)] − [0.0001 (weight^2)] ($R^2 = .56$). A regression line with 95% confidence interval is shown.

RESULTS

A group of 225 children were initially evaluated, 184 of whom were included in the final analyses. Five children were excluded because of movement during DPA scanning, and 36 were excluded because their weights or heights were above the 95th percentile or below the fifth percentile for their ages. Eighty-three girls (45.1%) and 101 boys (54.9%) were measured. There were 99 white (53.8%), 45 black (24.5%), and 40 Hispanic (21.7%) children. An educational profile of the head of the household revealed that 60% of the parents had a high school education or lower, 19.3% had attended college for at least 1 year but had not received a degree, and 20.7% had a college degree or higher.

The median and range of BMDs for each group studied are shown in Table 1. All measured and calculated data except percent of body fat and cross-sectional arm area correlated with BMD (Table 2). Bone mineral density correlated with body weight ($r = .746$; $P < .0001$), lean body mass ($r = .725$; $P < .0001$), height ($r = .693$; $P < .0001$), total body fat ($r = .642$; $P < .0001$), body mass index ($r = .591$; $P < .0001$), age ($r = .580$; $P < .0001$), and triceps skinfold thickness (r = .358; $P < .0001$).

A quadratic equation using weight as the independent variable best described BMD: BMD = 0.3209 + [0.0168(weight)] − [0.0001(weight^2)] ($R^2 = .56$) (Figure). A linear regression (not shown) using weight as the only variable was almost as good as the quadratic function in describing the observations ($R^2 = .55$). Transformations (log and exponential) of BMD and all other measured variables did not significantly increase the R^2 value of a given regression equation for describing BMD.

COMMENT

The data presented here demonstrate that body weight, height, and age are highly correlated with spinal L-2, L-3,

Table 1.—Median and Ranges for Bone Mineral Density (BMD) and Weight in 184 Normal, Healthy 5.00- Through 11.99-Year-Old Black, White, and Hispanic Children Grouped by Age

Age, y	No. of Subjects (N=184)	Median (Range) BMD (L2-4) g/cm^2	Median (Range) Weight, kg
5-5.99	12 (F)	0.644 (0.492-0.824)	20.2 (17.1-32.8)
	14 (M)	0.610 (0.499-0.713)	20.1 (15.1-23.7)
6-6.99	12 (F)	0.640 (0.539-0.705)	22.9 (19.5-28.3)
	20 (M)	0.659 (0.519-0.772)	22.4 (18.4-35.0)
7-7.99	11 (F)	0.716 (0.533-0.805)	26.5 (23.7-34.2)
	15 (M)	0.648 (0.560-0.796)	24.0 (19.0-28.3)
8-8.99	15 (F)	0.689 (0.550-0.931)	26.7 (19.2-37.2)
	15 (M)	0.694 (0.529-0.782)	27.6 (20.6-34.8)
9-9.99	12 (F)	0.727 (0.579-0.833)	29.0 (24.3-41.9)
	11 (M)	0.717 (0.667-0.804)	32.2 (25.8-36.1)
10-10.99	10 (F)	0.784 (0.628-0.936)	40.3 (26.0-53.0)
	14 (M)	0.703 (0.602-0.838)	33.3 (25.5-49.8)
11-11.99	11 (F)	0.838 (0.724-1.149)	46.8 (33.5-55.6)
	12 (M)	0.793 (0.636-0.899)	40.6 (30.6-49.6)

Table 2.—Spearman's Rank Correlation Coefficients (r) for Bone Mineral Density vs Directly Measured and Derived Variables (N = 184)

Variable (x)	r	P
Weight	.74571	<.0001
Lean body mass	.72528	<.0001
Weight/height	.71903	<.0001
Weight^2/height^2	.71903	<.0001
Height	.69314	<.0001
Midarm circumference	.68484	<.0001
Total body fat	.64171	<.0001
Body mass index (weight/height^2)	.59125	<.0001
Age	.57960	<.0001
Weight percentile	.41257	<.0001
Triceps skinfold	.35776	<.0001
Arm muscle area	.27845	<.0001
Skinfold percentile	.24383	.0009
Percent body fat	.06498	.3808

and L-4 BMD in children aged 5.00 through 11.99 years. Glastre et al[11] recently reported data on spinal BMD in 135 healthy children measured by dual energy x-ray absorptiometry. They found correlations between spinal BMD and patient age, weight, and height that are similar to those reported here. As discussed by Specker et al,[4] weight, height, and age are strongly correlated variables, making it impossible to separate the individual effects of each on BMD. We have reported the correlations of BMD with lean body mass, total body fat, body mass index, percent of body fat, and several other indexes (Table 2). However, one must be cautious when interpreting the results of correlations of BMD with derived variables because the equations used to derive these values were generated from different populations of children than those studied here. In addition, several of these variables are calculated from weight and height.

Data show that a relatively wide range of BMD values are found in healthy children. Interestingly, BMD is associated more strongly with body weight than with age. In the child, the data suggest that spinal mineralization is more responsive to load bearing, reflected by body weight, than to the chronologic age of the child. This might make interpretation of spinal BMD data difficult in the child who is underweight for age. The observed BMD might be in a range found in children with metabolic bone disease. Further studies are needed to define the differences and diagnostic significance (if any) between "normal" and "abnormal" populations in regard to spinal BMD. Larger populations must be studied to determine the normal range for spinal BMD in growing children and adolescents.

A preliminary evaluation of our data suggested that significant racial and sexual differences in spinal BMD might exist in children and adolescents. Spinal BMD dimorphisms in children measured by SPA have been reported at other sites.[4,5] We are currently evaluating a larger group of children and adolescents to determine if significant dimorphisms in spinal BMD are present.

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Special Features

Radiological Cases of the Month

John Grosso, MD, Charles M. Myer, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

An 8-month-old male infant presented to his pediatrician with a 12-hour history of fever, irritability, decreased oral intake, and symptoms consistent with an upper respiratory tract infection. The child had a temperature of 38.8°C rectally and was tachycardic, with a heart rate of 160 beats per minute. The patient's physical examination was remarkable for mild neck tenderness and rigidity and right-sided enlarged cervical nodes. The tympanic membranes were dull and erythematous bilaterally. The oropharynx was full, with erythema of the right posterior pharyngeal wall. The patient's white blood cell count was 20×10^9/L with a left shift. A lateral neck roentgenogram (Fig 1) was obtained followed by a computed tomographic scan of the neck (Fig 2).

The patient was admitted to the hospital and treatment was started with cefuroxime axetil (100 mg/kg per day). He subsequently developed stridor and progressive respiratory distress requiring emergent intubation. On examination in the operating room there was a large fluctuant mass in the right posterior pharyngeal wall. Incision and drainage of the abscess were performed and the patient remained intubated for 48 hours. The examination in the operating room at the end of that time demonstrated resolution of the abscess, and the patient was extubated. Intravenous antimicrobial therapy was continued for 5 days and the infant was discharged home to be treated with amoxicillin/clavulanate potassium (40 mg/kg per day) for 1 week.

The first case of retropharyngeal abscess (RPA) was reported by Galen[1] in the second century. Although mor-

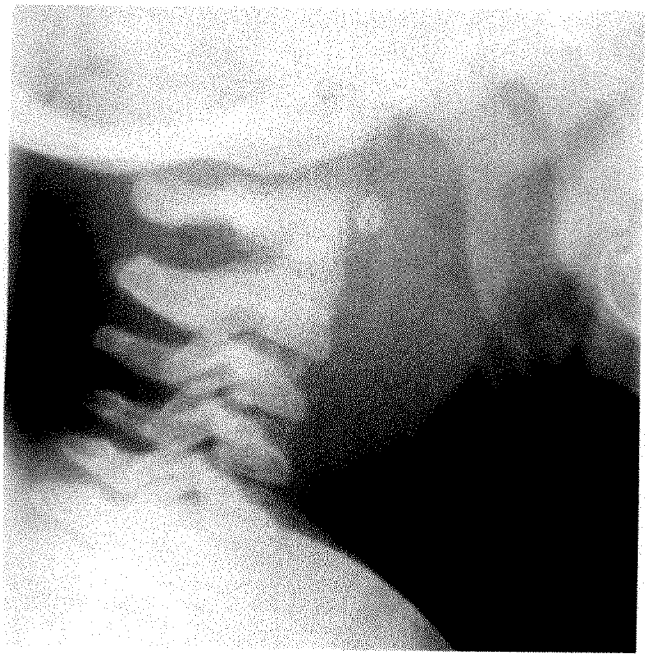

Figure 1.

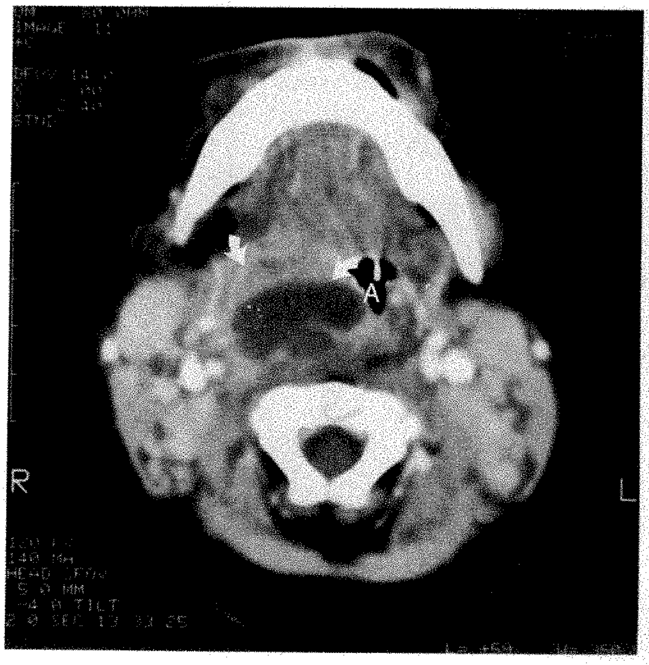

Figure 2.

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Contributed from the Department of Otolaryngology and Maxillofacial Surgery, Division of Pediatric Otolaryngology, Children's Hospital Medical Center, Elland and Bethesda Avenues, Cincinnati, Ohio.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

Retropharyngeal Abscess

Fig 1.—Lateral neck roentgenogram shows widened retropharyngeal soft tissues.

Fig 2.—Computed tomography of the neck demonstrates a large, right, peritonsillar and retropharyngeal abscess (arrows) causing division of the airway (A) to the left and airway compression.

tality from an RPA has been significantly reduced since the advent of antimicrobial therapy in the 20th century, a delay in diagnosis and treatment still leads to significant morbidity and mortality.

The retropharyngeal space is located within two layers of deep cervical fascia anterior to the spine and posterior to the pharynx. It extends from the skull base to the level of the carina.[2] The retropharyngeal space contains adipose tissue, lymphatics, and lymph nodes, which drain the nose, paranasal sinuses, nasopharynx, soft palate, and eustachian tube.[3] An infectious process in any of these regions may spread via lymphatic channels to the nodes in the retropharyngeal tissue. Lymph node infection may lead to the formation of a local abscess. In addition to the lymphatic spread of infection to the retropharyngeal space, infection may be the result of direct extension from contiguous areas. For example, following otitis media the infection may spread inferiorly through the skull base into the retropharyngeal tissues. Trauma to the posterior oropharynx from endoscopic procedures or penetrating trauma may also lead to an infection in this area.

Lymphatic spread of infection to the retropharyngeal space is the most common cause of an RPA in children. It should be noted that the retropharyngeal nodes usually regress by age 5 years, making lymphatic spread of infection a less likely cause of an RPA in older children or adults.[4]

A child with an RPA frequently has a history of a recent upper respiratory infection. Fever, irritability, decreased oral intake, and drooling are early symptoms. As the RPA enlarges, upper airway obstruction occurs, with symptoms of stridor and respiratory distress. A physical examination usually reveals an erythematous oropharynx with a unilateral fullness or bulging of the posterior pharynx. Although the abscess mass is fluctuant, palpation of an RPA is not recommended in children because of the risk of rupturing the abscess with consequent aspiration.

The medical history and physical examination are important in the diagnosis, although a thorough examination may be difficult in a young child with an RPA. A lateral neck roentgenograph is noninvasive, rapid, and provides useful information in the diagnosis of an RPA. Wholey et al.[5] have established norms for the width of the retropharyngeal space by roentgenography. In general, the retropharyngeal space is no wider than the width of the adjacent vertebral body of C-4.[6] In addition to widening on lateral roentgenography, gas or a gas-fluid level may be present in the retropharyngeal space. If the findings on physical examination and lateral neck roentgenography are equivocal, a computed tomographic scan of the neck, examination of the oropharynx under general anesthesia, or an ultrasonographic examination is indicated.

An RPA is a surgical emergency. Initial management must be directed at stabilizing the patient's airway. Emergent endotracheal intubation or tracheotomy may be necessary and should be done under controlled conditions, if possible. Antimicrobial therapy is empiric, directed at the most common organisms involved in an RPA (ie, group A β-hemolytic streptococcus, *Streptococcus viridans*, and *Staphylococcus aureus*) and may be later modified according to culture and sensitivity results. Although antimicrobial therapy is important, an essential aspect of treatment is incision and drainage. This is usually performed intraorally under general anesthesia, but it may also be performed through an external lateral cervical approach.[7]

A complication of an RPA is rupture with aspiration and subsequent pneumonia.[8] The infection may also propagate inferiorly, producing mediastinitis, which carries an extremely high mortality rate. Spread may occur to the carotid sheath and cause internal jugular vein thrombosis or erosion of the carotid artery. As previously described, upper airway obstruction is a potential complication of an RPA.

An RPA should be part of the differential diagnosis in any young child with a history of swallowing or upper airway respiratory difficulties. The complications of an RPA are significant, and an accurate diagnosis and appropriate treatment for this condition will lower the associated morbidity and mortality.

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Yakov Sivan, MD; Marvin D. Nelson, Jr, MD; Sharon Lee, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A 3-year-old boy with known congenital heart disease was admitted to the hospital in respiratory distress. Cyanotic at birth, he was found to have D-transposition of the great vessels for which an immediate atrial septostomy was performed. At 14 months of age, a Mustard procedure was accomplished without apparent complication. A neurologic examination at 18 months of age revealed mild right hemiparesis and developmental delay. A brain computed tomographic (CT) scan demonstrated old left paraventricular and left occipital infarcts.

The patient's respiratory distress was identified as pulmonary vascular congestion and interstitial edema secondary to obstruction of the surgical intracardiac baffle.

During the surgery to repair the baffle, the boy suffered a brief cardiac arrest while being placed on the cardiac bypass pump. Following surgery he failed to regain consciousness. On neurologic examination, his pupils were midsize and reactive to light, and his deep tendon reflexes were hyperactive. A CT head scan without contrast material was obtained (Fig 1).

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Contributed from the Departments of Pediatrics (Drs Sivan and Lee) and Radiology (Dr Nelson), Childrens Hospital of Los Angeles, University of Southern California School of Medicine.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

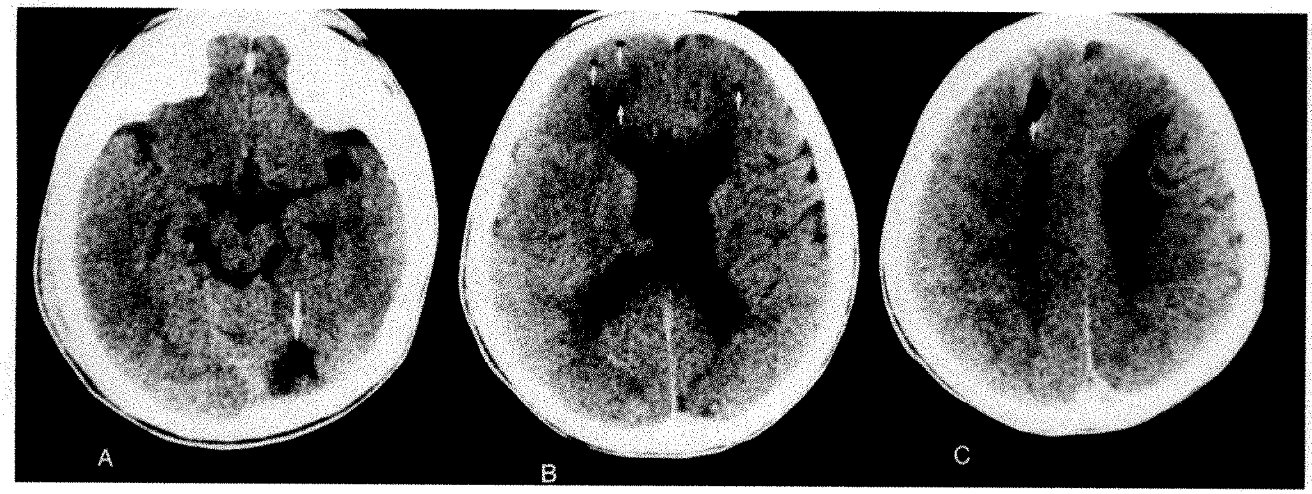
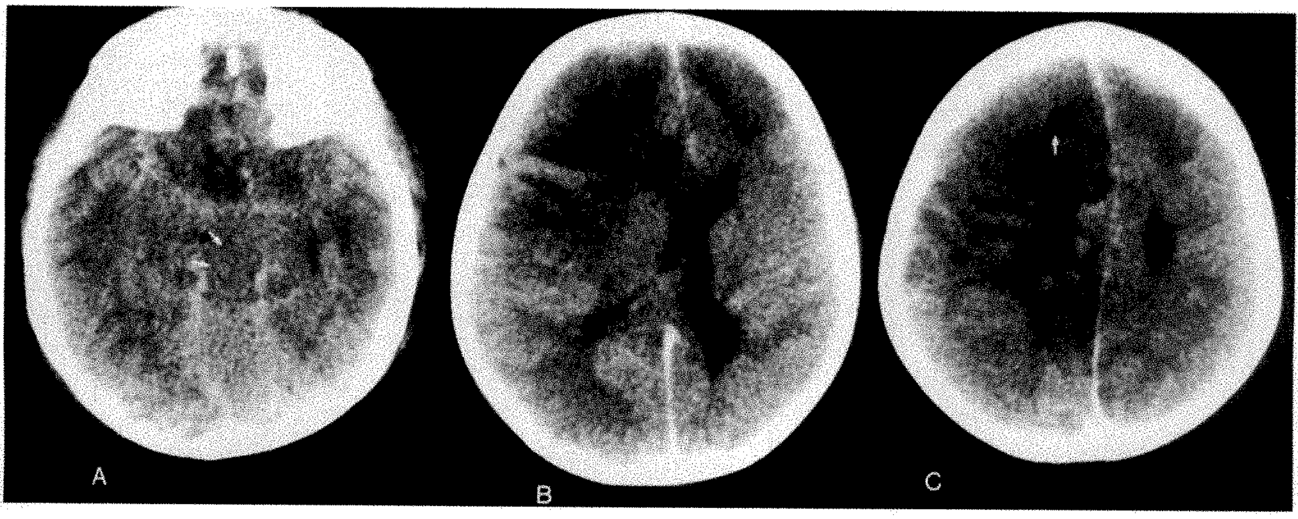


Figure 1.

Figure 2.



Denouement and Discussion

Cerebral Air Embolism

Fig 1.—Nonenhanced computed tomographic head scan. Left, Old occipital infarct (arrow). Center, Small focal collections of air within the parenchyma of the right and left frontal lobes (arrows). The lateral ventricles are mildly enlarged. Right, Large collections of air in the right frontal lobe (arrow).

Fig 2.—Nonenhanced computed tomographic head scan 12 hours after the one shown in Fig 1. Left, Diffuse cerebral edema showing loss of basal cisterns and compression of midbrain (arrows). Compare with Fig 1, left. Center, Bifrontal and right parietal infarctions with edema compressing the right lateral ventricle, causing right to left midline shift. Right, Residual pocket of air (arrow) within the infarcted right frontal lobe.

Apparently, air entered the vascular system, passed up the carotid arteries, and embolized multiple cerebral arteries.

Immediately following the first CT scan, the patient was placed on hyperventilation and diuretic therapy was begun. His neurologic status did not improve and responses to noxious stimuli became weak. Several left-sided convulsive episodes occurred. Twelve hours later the patient became unresponsive, his pupils became nonreactive, and brain-stem reflexes were absent. A brain CT scan showed extensive infarctions of both cerebral hemispheres, with severe cerebral edema, loss of the basal cisterns, and effacement of the midbrain suggesting transtentorial herniation (Fig 2). An increase of mannitol, diuretics, and extreme hyperventilation failed to improve the patient's condition. An isotope cerebral blood flow study showed no cerebral perfusion and the patient was pronounced dead. A request for an autopsy was denied.

Cerebral air embolism results from air bubbles lodging in cerebral arteries, producing a transient vascular block. The embolus stimulates arterial spasm, which is followed by vascular dilation and transitory stasis of flow.[1,2] Ultimately, the air bubbles move through the capillary bed and dissipate in the venules.

Cerebral air embolism may occur following pneumothorax, open heart surgery, cardiopulmonary bypass surgery, neurosurgery, arterial or venous catheterization, hemodialysis, and scuba diving.[3-8] Air may pass directly into the arterial system when a congenital heart condition results in a right to left shunt. Any surgical procedure directly involving the large vessels may result in embolism.

Air may also pass from the venous to the arterial system via arteriovenous anastomoses in the lung or via the foramen ovale.[9-10] The presumed mechanism is that an initial pulmonary venous embolism raises the right atrial pressure, which opens a normally closed foramen ovale, allowing air to pass into the left atrium.

Clinically, cerebral embolism produces sudden depression in the level of consciousness, with progression to coma. Generalized seizures are common. The degree of neurologic dysfunction is influenced by the location of the air bubbles and the degree of ischemia and edema that results.

Therapy consists of aggressive management of the seizures and cerebral edema. Hyperbaric oxygen has been tried with some success.[11] Hyperbaric oxygen theoretically enhances the absorption of free air by washing nitrogen out of the air collections. The high barometric pressure helps to reduce the size of the air bubbles by compression.

Roentgenographically, CT is the best method of establishing the diagnosis.[3-8] Multiple small, well-defined, very-low-attenuation areas of air density are seen within the brain parenchyma and extracerebral spaces. Focal or diffuse areas of ischemia/infarction may be seen. A normal initial CT scan does not exclude the diagnosis, and follow-up scans in 48 to 72 hours are recommended.[3-7] The pockets of air are absorbed over several days.[4]

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Picture of the Month

Kip R. Hartman, MD, James S. Rawlings, MD (*Contributors*);
Murray Feingold, MD (*Section Editor*)

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Contributed from the Department of Hematology, Walter Reed Army Institute of Research, Washington, DC.
Reprint requests to the National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

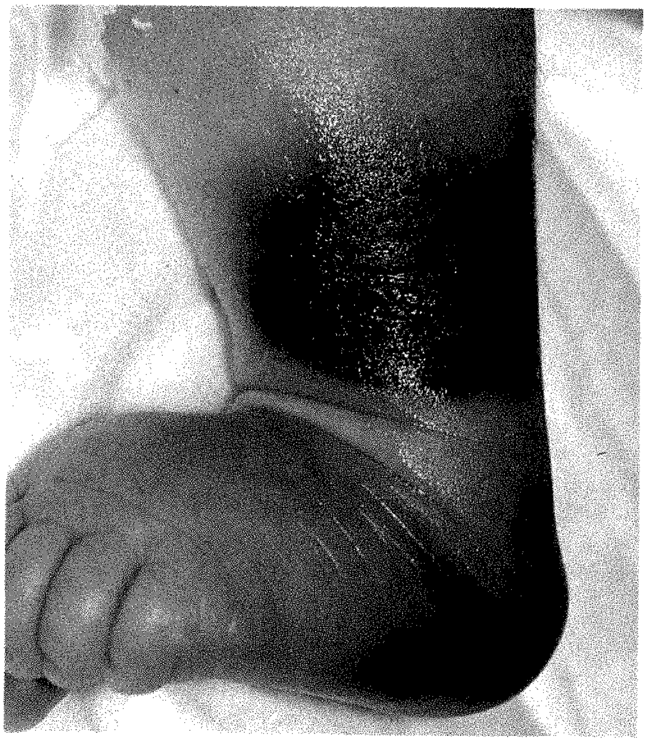

Figure 1.

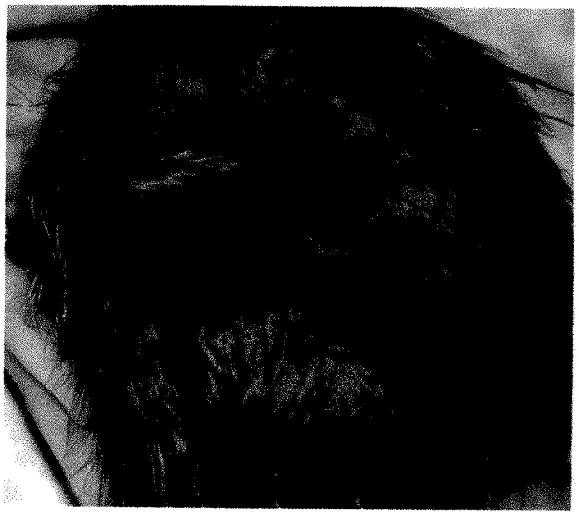

Figure 2.

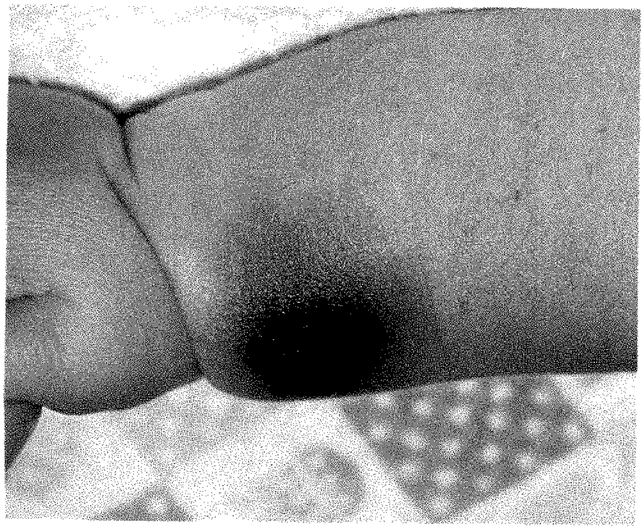

Figure 3.

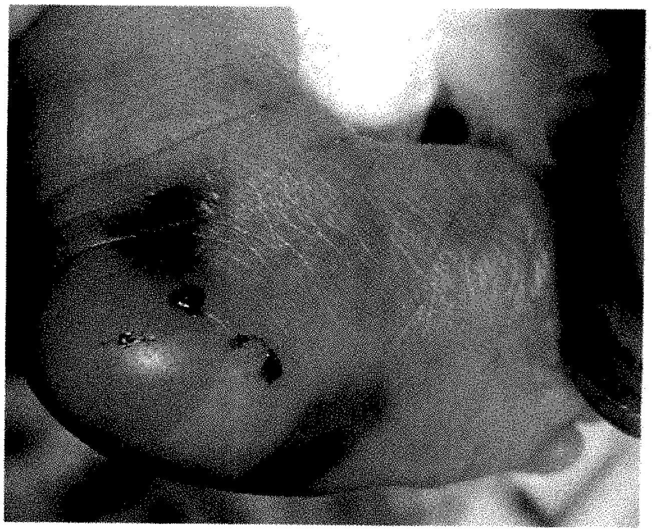

Figure 4.

Denouement and Discussion

Protein C Deficiency

Figs 1 through 4.—Purpura fulminans–like thrombotic skin lesions in a newborn with complete (homozygous) protein C deficiency.

Manifestations

Protein C, produced by the liver, is essential in the regulation of coagulation and is a vitamin K–dependent proenzyme. A proenzyme is an inactive precursor that is converted to an active enzyme by the action of acid, another enzyme, or by other means. Protein C rapidly inactivates the active forms of V and VIII, resulting in an inhibited coagulation process. In the absence of protein C, thromboses (venous and microvascular) and skin necrosis take place. Skin necrosis usually occurs during the first 2 to 12 hours after birth, and consists of ecchymotic areas that progress to indurated purple-black lesions with central bullae and peripheral erythema. They occur most commonly in the scalp (associated with vertex presentation deliveries), buttocks, and areas in which there is soft-tissue trauma due to pressure. The lesions are similar to the skin lesions present in warfarin-induced necrosis of the skin.

Other findings that may be present at birth in the absence of protein C include brain infarction; hydrocephalus; and eye lesions consisting of new and old vitreous hemorrhages, microphthalmia, and persistent hyperplastic primary vitreous. Deep venous thromboses may occur, such as renal vein thrombosis.

Laboratory findings show evidence of disseminated intravascular coagulopathy including increased prothrombin time and partial thromboplastin time, and decreased amounts of fibrinogen. The platelet count is usually elevated. Diagnosis is established by finding essentially undetectable amounts of protein C function activity, low or undetectable amounts of protein C antigen, and decreased protein C in both parents.

Genetics

This disorder is transmitted in an autosomal recessive manner, and heterozygous parents may have a history of recurrent venous thromboses during childhood. Reduced protein C antigen and protein C are present in carrier parents.

Treatment

Treatment includes infusion of fresh-frozen plasma every 12 hours. Oral warfarin anticoagulation therapy has been successful in controlling recurrent thromboses in some patients.[1] Diagnosis and treatment of this condition may be life saving, and decreases the morbidity associated with ongoing thromboses.[2] Patients who receive warfarin therapy must be closely monitored because of the side effects associated with this drug, including the risk of hemorrhage. Ophthalmologic follow-up is also important because of potential eye damage secondary to hemorrhage, thrombosis, and retinal detachment. Genetic counseling should be provided.

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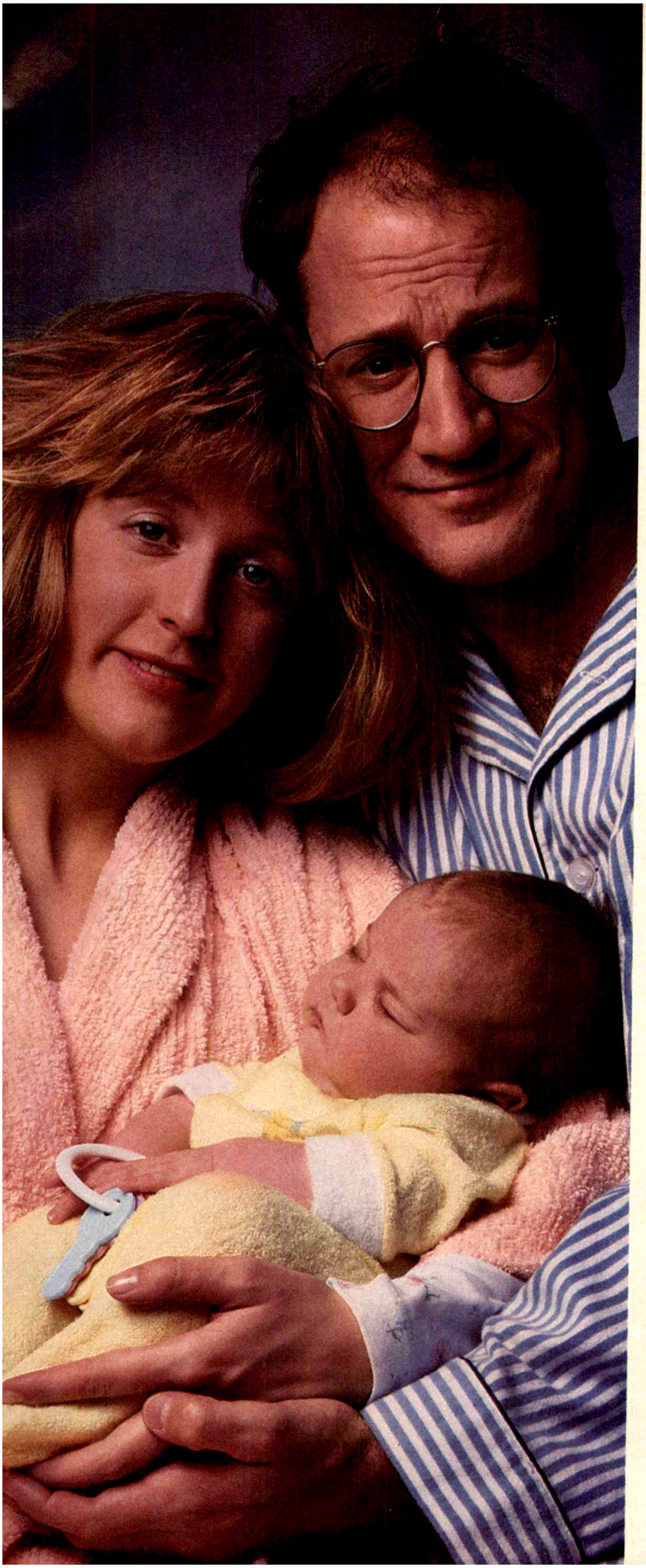
The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.



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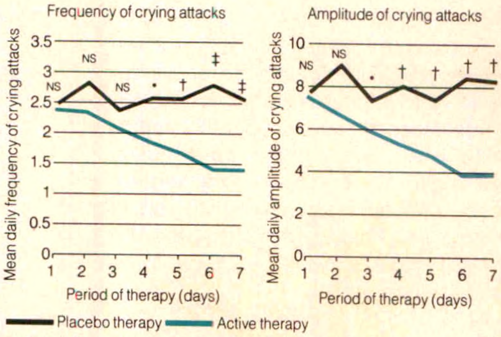

p values (active vs. placebo) NS = Not significant •$p < 0.05$ †$p < 0.02$ ‡$p < 0.01$

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PZ24

Resident Training in Community Pediatricians' Offices

Not a Financial Drain

Janice R. Sargent, PhD, Lucy M. Osborn, MD

• There are numerous disadvantages to teaching ambulatory pediatrics in hospital-based clinics. The present study evaluated the economic impact on community pediatricians' practices that served as continuity experience sites for pediatric residents by using an apprenticeship model. The number of patients seen and the dollars billed by preceptors were not negatively affected by the presence of a resident, even though these preceptors provided significantly more supervision to residents than that received by residents in hospital-based clinics. Furthermore, residents billed substantial revenues for preceptor practices. This approach to teaching general pediatrics is economically viable, providing resident stipends are not dependent on fees generated by patient visits.

(*AJDC*. 1990;144:1356-1359)

Medical training through the 19th century was accomplished almost exclusively through apprenticeships. However, the focus of medical education shifted in the 20th century to group teaching in hospital settings. While there are ample opportunities for trainees to acquire expertise in the diagnosis and management of medical problems that require hospitalization, training in ambulatory medicine has often been neglected. Perkoff[1] discussed several reasons for interest in teaching clinical medicine in ambulatory settings: the trend for only the sickest patients to be seen in hospitals, changes in hospital economics that limit the lengths of stay of patients, declining patient populations in hospital-based clinics, and the need for primary care physicians who require different training experiences. Awareness of such factors have led recently to an increased emphasis in outpatient training in the departments of family practice, internal medicine, and pediatrics. While this emphasis has allowed both a different context and process for training in general medicine, educators[2-4] have questioned the adequacy of ambulatory teaching in hospital settings.

Outpatient clinic rotations and continuity clinics, where the resident establishes ongoing care of his or her own panel of patients, provide the major experiences for ambulatory pediatric training. Although the continuity clinic experience is intended to simulate a general pediatric practice, there are serious limitations in this approach, particularly in hospital-based clinics. However, economic concerns have been a significant obstacle to the consideration of alternative sites for continuity experiences. There are reports of the establishment of ambulatory clinics independent of hospital administration[5] as an alternative to hospital-based outpatient clinics and brief office rotations to acquaint pediatric residents with the realities of the general pediatric practice,[6] but no reports, to our knowledge, of any programs using community pediatricians' offices as continuity sites. Data reported from other medical disciplines or from other sites give conflicting impressions of the economic viability of nonhospital-based clinics, as training sites vary and methods for calculating costs are not uniform.[7-10]

The present study evaluated the economic impact on community pediatricians' practices that served as continuity sites for pediatric residents.

DESCRIPTION OF THE PROGRAM

Consideration of practicing pediatricians' offices as continuity experience sites in the residency training program at the University of Utah, Salt Lake City, resulted, in part, from a study that contrasted the patient population within our hospital-based clinics with those of community pediatricians.[11] Results of the study revealed that residents in our hospital-based clinics saw, almost exclusively, infants and young children for well-child care. In addition, the low patient volume was insufficient for residents to master the diagnosis and management of many common medical problems or behavioral-emotional problems that constitute a large portion of the general pediatrician's practice. Furthermore, residents were rarely observed in the course of conducting patient visits. In an attempt to provide a training experience that more closely resembled a general pediatric practice and to increase the amount of direct teaching, we initiated a pilot project that used the apprenticeship model.

From 1984 to 1986, two pediatric residents were assigned to a group practice for their continuity experience. After 1 year, we had established that the mechanics of such an approach were workable: patient volume was acceptable, the pediatricians were able to arrange their schedules to allow for supervision of the residents, nurses and office staff were supportive, and parents were accepting of having their children seen by a resident. However, the problem of financing such an undertaking remained unsolved.

In 1985, the Department of Pediatrics at the University of Utah was awarded a Primary Care Residency Training Grant from the Department of Health and Human Services, Rockville, Md. The first four residents entered the program in 1986, followed by four more in both 1987 and 1988. There are several unique characteristics of the primary care track, particularly the concept of apprenticeship. Each primary care resident is matched to a practicing community pediatrician for the continuity component of training. The community pediatrician serves as preceptor to the resident, initially being fol-

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Reprint requests to Department of Pediatrics, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132 (Dr Sargent).

lowed by the resident, then observing the resident conducting patient visits, and finally serving only as a consultant during the final stages of the residency. To enhance the continuity experience, primary care residents see patients in the community offices 2 half days per week in their first year and 3 half days during their second and third years, compared with only 1 half day per week for the residents in the core track.

The preceptors, who are members of the university clinical faculty, make a commitment to all 3 years of the residency and also agree to make time available to their "apprentice" for didactic discussion, supervision, observation and immediate feedback, and ongoing consultation. A series of seminars for the preceptors presents methods and approaches to effective teaching via this model. The pediatrician's office and nursing staff take on increased responsibility as the resident becomes akin to a junior partner in the practice. Individual and group meetings are held with the office staffs and nurses during the year to acquaint them with the program and data collection, to facilitate problem solving, and to give them an opportunity to share ideas with one another. All funds generated by the resident patient visits are collected and retained by the individual practices.

While the educational advantages of such an apprenticeship model seem to be obvious, we were interested in assessing the financial impact that such an arrangement had on the practices. Although funds were available initially to reimburse the preceptors for their time, we hoped that we could demonstrate that there was no negative economic impact on the practices so that this component of the training program could eventually become self-supporting.

METHODS

The economic impact of the preceptors' practices was assessed by comparing the number of patients seen and the amount billed per half day by the preceptors at times when the residents were present and at times when the residents were not present in the offices. Data were collected on 4 half days per month, ie, 2 when the resident was in the office and 2 when the resident was not in the office. Each preceptor provided, in advance, 2 half days when the resident was not present that matched as closely as possible the half days when the resident was present in the number of preceptor hours worked and typical patient load. Data were collected every month during the first year of the program (1986 to 1987) and every other month during subsequent years (1987 to 1989).

Financial impact was also assessed by examining the fees generated by the resident for patient visits. During the first year of the program (1986 to 1987), residents kept a daily log of every half day in their preceptor offices that included the number of patients seen and the amount billed. These data were collected every other month during subsequent years (1987 to 1989).

Table 1.—Average Number of Patients Seen by Preceptors per Half Day*

	Mean ± SD (n)		
	With Residents	Without Residents	P†
PL-1s	14±6 (121)	14±5 (128)	.57
PL-2s	13±5 (62)	14±5 (71)	.62
PL-3s	17±6 (24)	17±7 (25)	.81
Total	14±6 **(207)**	14±5 **(224)**	.46

*PL-1s indicates first-year residents; PL-2s, second-year residents; and PL-3s, third-year residents.
†Comparisons using *t* tests.

Table 2.—Average Dollars Billed by Preceptors Only per Half Day*

	Mean ± SD (n)		
	With Residents	Without Residents	P†
PL-1s	368±166 (121)	392±152 (128)	.23
PL-2s	390±144 (62)	392±134 (71)	.94
PL-3s	452±182 (24)	417±165 (25)	.49
Total	384±163 **(207)**	395±148 **(224)**	.48

*See Table 1 footnotes for explanation of PL-1s, PL-2s, and PL-3s.
†Comparisons using *t* tests.

RESULTS

Preceptors completed a total of 431 reports of half days throughout the 3-year period, 1985 to 1989: 207 reports for half days when residents were in their offices and 224 reports for half days when residents were not in their offices. These combined data represent the number of patients seen and the amount billed by the preceptors for all 3 completed years of residency training: 3 years of first-year residents (PL-1s), 2 years of second-year residents (PL-2s), and 1 year of third-year residents (PL-3s). Table 1 presents the average number of patients seen by preceptors per half day with and without residents in the offices for each level of residency training and for the years combined. Comparing the number of patients seen by the preceptors with and without residents present by year of training and the total by using a t test revealed that there were no significant differences. However, preceptors did see a greater number of patients when supervising the PL-3s than when supervising PL-1s or PL-2s ($F = 3.45$, $P = .03$).

Table 2 presents the average dollars billed by preceptors *only* per half day with and without residents in the offices for each level of residency training and for the years combined. On average, preceptors billed $384 on half days with residents in their offices and $395 on half days without residents in their offices, a difference that is not significant. Because more supervision is required in the first year of the apprenticeship and therefore might be expected to interfere most with the preceptor's practice, we examined these preceptor data separately based on the level of residency training. Although preceptors supervising PL-3s billed more than when supervising PL-1s, this difference was not statistically significant.

During the third year of the program, preceptors were additionally asked to report the number of hours worked for half days with and without residents in their offices. These data are presented in Table 3 and represent hours worked by preceptors with residents at all levels of training. Preceptors reported that they worked an average of 3.2 hours per half day with residents in their offices and 3.1 hours per half day without residents in their offices, a difference that is not significant. Comparisons of hours worked by the level of residency training were not statistically significant.

Even though preceptors reported

Table 3.—Average Number of Hours Worked by Preceptors per Half Day*

	Mean ± SD (n)		
	With Residents	**Without Residents**	**P†**
PL-1s	3.2±0.7 (28)	3.2±0.6 (32)	.74
PL-2s	3.1±0.8 (28)	3.1±0.9 (27)	.92
PL-3s	3.3±0.9 (20)	2.9±0.6 (21)	.09
Total	3.2±0.8 **(76)**	3.1±0.7 **(80)**	.50

*See Table 1 footnotes for explanation of PL-1s, PL-2s, and PL-3s.
†Comparisons using *t* tests.

Table 4.—Average Dollars Billed by Residents Only per Half Day*

	Mean ± SD (n)		
	1986-1987	**1987-1988**	**1988-1989**
PL-1s	118±59 (140)	157±111 (334)	115±68 (83)†
PL-2s	...	155±75 (147)	159±93 (74)†
PL-3s	...	...	158±76 (210)

*See Table 1 footnotes for explanation of PL-1s, PL-2s, and PL-3s.
†Represents only first half of year.

that they were able to see and bill for equivalent numbers of patients, and not spend significantly more time per half day with residents in the offices, preceptors provided substantial supervision of resident visits. The daily record sheets included information on the degree of supervision provided by the preceptor for every patient visit whether (1) the preceptor observed most of the entire visit conducted by the resident or (2) the preceptor served as a consultant, which included a case presentation or partial observation by the preceptor. Data collected from the first year of the program revealed that primary care residents were observed by their preceptors for at least one entire patient visit on 29% of the half days that they were in the offices, compared with 15% of the half days for traditional residents in hospital-based clinics ($\chi^2 = 13.73$, $P<.001$).

Billings were also tabulated for half days by the residents on the daily record sheet. Table 4 presents the dollars billed by the residents *only* per half day separately for each group of residents and the level of training. Extrapolating from the amounts billed by the three groups of PL-1s, based on 2 half days per week and 49 weeks per year, PL-1s in this program billed between $11 270 and $15 386 on the average annually for the preceptors' practices. Based on 3 half days per week and 49 weeks per year, PL-2s billed between $22 785 and $23 373 and PL-3s billed $23 226 on the average annually for the preceptors' practices.

COMMENT

Examination of the preceptor and resident billing data indicated that the presence of a resident in the private office setting did not place the preceptors at financial risk. Kahn et al[10] reported a similar result with a senior pediatric resident in a prepaid group practice. Even though patient volume was low, they determined that there was no cost to the practice and that the benefit of the services rendered to patients by the resident compensated for the preceptors' time spent in teaching. However, the value of the services rendered by the resident was not sufficient to account also for the resident stipend or to pay overhead or program administration costs. Our results indicated that even PL-1s generated substantial billings for preceptors' practices and their presence did not jeopardize the preceptors' ability to continue to see and bill for services for his or her own patients.

Pawlson and Watkins[9] also found that family practice residents in a community-based prepaid practice provided services that came close to being self-sustaining for that part of the program, but were insufficient to support the entire ambulatory care portion of the training program. Both Goodson et al[7] and Stern et al[8] have reported on the hospital-based group practices associated with the Internal Medicine Program at Harvard Medical School, Boston, Mass. They concluded that resident revenues are not sufficient for the support of the ambulatory part of their training program and that external financial support is needed. It is more difficult for us to assess the exact value of our resident revenues as preceptors were not in prepaid practices, and we cannot determine the actual collections for resident patient visits. However, even if collection rates were modest, residents generated substantial revenues for the preceptor practices.

Demonstration that preceptor and resident billings, in an apprenticeship model, can support preceptor time and not place the preceptor at an economic disadvantage is a significant finding. The present investigation sought to determine if private practitioners' offices were viable sites for continuity experiences, both educationally and economically, and did not require that resident billings support the entire ambulatory component of training nor resident stipends. Although each preceptor was awarded $7500 the first year of the program, decreasing funds prohibited a continuation of this award. During the second year of the program, the preceptors were made aware of the limited funds and decided that the preceptor awards should be greatest when precepting a PL-1 and least when precepting a PL-2. During the third year of the program, preceptors of PL-1s were given $6667, preceptors of PL-2s were given $4998, and preceptors of PL-3s were given $3332. These awards seemed to be crucial when recruiting preceptors for the first year of the program, but have not appeared to be a major factor in the continued commitment of preceptors or recruitment since the risks and benefits of the program have been delineated.

Pawlson and Watkins[9] have discussed the economic considerations of training programs for alternative sites to hospital-based clinics: overhead costs of the practice, reimbursement for preceptor time, and out-of-pocket expenses, including resident stipends. The results of the present study revealed that overhead costs to the practices were compensated for by the resident patient revenues. Because the residents were in the practices only 2 or 3 half days per week, they could be scheduled at times when examination rooms were available, usually when partners in the practice had days off, thereby alleviating the necessity for expanding office space. Similarly, because each practice had only one resident (except for two large group practices), the office and nursing staffs were able to accommodate the needs of the resident, and no additional support personnel were hired by any of the preceptors. Thus, an additional advantage to the apprenticeship model is that an individual resident, working part-time, creates minimal disruption to the regular functioning of the preceptor's office.

Data indicating that preceptors were able to maintain a consistent level of billing for services when residents were in their offices, in addition to collecting revenues from the resident billings, demonstrates that preceptor teaching time and other commitments to the training program can be reimbursed by using this program model. Because our data indicated that residents in these practices were observed by preceptors approximately twice as often as residents in our hospital-based clinics, we were interested in how the preceptors were able to continue billing at a consistent rate. Discussion with the preceptors suggested that patient scheduling was a major factor. Preceptors reported that for half days when residents were in their offices, preceptors saw fewer children for well-child care, which is both more time-consuming and remunerated at a lower rate, and saw more acute illness visits. This allowed them to be more available to the residents for consultation and supervision while seeing a significant number of patients themselves.

Data from the resident billings indicated that residents did not produce sufficient income to support their stipends. During the study period, resident stipends ranged from \$21 850 for PL-1s to \$26 400 for PL-3s. Thus, our findings corroborated the findings of other investigators who have documented the need for external funding for ambulatory training.[7-10]

Our results indicated that the educational advantages of the apprenticeship model need not be dismissed due to economic considerations. On the contrary, it can be of financial advantage to precept a resident.

This study was supported by grant 5D28 PE 18085 from the Department of Health and Human Services, Washington, DC.

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Book Review

Books Received but Not Reviewed, 1989

Prenatal Abuse of Licit and Illicit Drugs, edited by D. E. Hutchings, 388 pp, \$97, New York, NY, The New York Academy of Sciences, 1989.

Preventive Health Services for Adolescents, by J. S. Wodarski, 223 pp, \$40.75, Springfield, Ill, Charles C Thomas Publisher, 1989.

Proceed With Caution, by N. A. Holtzman, 316 pp, \$37, Baltimore, Md, The Johns Hopkins University Press, 1989.

Rett Syndrome and Autism: Issues in Neurology Series, edited by R. H. Haas, I. Rapin, and H. Moser, 92 pp, \$25, Littleton, Mass, PSG Publishing Co Inc, 1988.

Roundmanship, '89, edited by B. B. Dan, R. D. Feigin, E. J. Quilligan, S. I. Schwartz, J. H. Stein, and J. A. Talbott, 243 pp, \$19.95, Chicago, Ill, Year Book Medical Publishers Inc, 1989.

Swenson's Pediatric Surgery, edited by J. G. Raffensperger, 978 pp, \$145, with illus, East Norwalk, Conn, Appleton & Lange, 1989.

Textbook of Paediatric Anaesthetic Practice, edited by E. Sumner and D. J. Hatch, 616 pp, \$79, Philadelphia, Pa, WB Saunders Co, 1989.

Thalassemia: Pathophysiology and Management, Part B, 500 pp, \$160, New York, NY, Alan R Liss Inc, 1988.

The Child With Cancer in the Community, edited by R. E. Dowell, Jr, D. R. Copeland, and J. van Eys, 141 pp, \$26.75, Springfield, Mass, Charles C Thomas Publisher, 1988.

The Complete Book of Pregnancy and Childbirth, by S. Kitzinger, 400 pp, \$18.95, with illus, New York, NY, Alfred A Knopf Inc, 1989.

Theories of Carcinogenesis, edited by O. H. Iversen, 327 pp, \$59.95, New York, NY, Hemisphere Publishing Co, 1988.

Toxicologic and Pharmacologic Principles in Pediatrics, edited by S. Kacew and S. Lock, 314 pp, \$59.50, New York, NY, Hemisphere Publishing Co, 1988.

What Shall We Tell the Kids? by B. Olshaker, 253 pp, \$8.95, New York, NY, Lynx Books, 1989.

Your Baby & Child From Birth to Age Five, by P. Leach, 553 pp, \$16.95, with illus, New York, NY, Alfred A Knopf Inc, 1989.

Youth, Exercise, and Sport, by C. Gisolfi and D. R. Lamb, 607 pp, \$40, Indianapolis, Ind, Benchmark Press, 1989.

Growth in Obese Children Treated for Obesity

Leonard H. Epstein, PhD; James McCurley, MA; Alice Valoski, MS, RD; Rena R. Wing, PhD

• This study assesses the growth patterns during a 5-year period in children aged 6 to 12 years treated for obesity using behavioral family-based treatment procedures. Previous studies have suggested a decrease in height velocity after weight reduction, but these results did not consider either the height of the parent or the greater height of obese than nonobese children. Results show that at entry, obese children are taller than their nonobese peers (74th percentile), and that even after 5 years, they remain taller than the norm (65th percentile). Child weight and level of physical maturity accounted for 54% of the variance in predicting baseline height percentile. Entrance height and parental height accounted for 9% of the variance in changes in height percentile, both adjusted for parental height. Weight change did not correlate with growth adjusted for parental height. These results do not suggest that negative effects on height are a long-term side effect of child weight control.

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Numerous benefits document the successful treatment of obesity in children, including such long-term goals as prevention of adult obesity and related diseases such as cardiovascular disease[1,2] and diabetes,[3,4] as well as short-term goals such as improvements in fitness,[5,6] blood pressure,[7] and serum lipid levels.[8] Despite the benefits of weight loss, the possible negative side effects of treatment must be considered. The most prominently discussed negative side effect probably is the effect of weight control on growth.[9] Treatment for obesity involves a diet sufficient to promote growth while concurrently decreasing excess body fat.[10] Despite the controversy between the benefits of treating childhood obesity and the potential for adverse effects of weight control on growth, limited long-term reports of the effects of weight control on growth in obese children have been published. Available research suggests that dieting in obese children can influence short-term growth.[11,12] However, catch-up growth occurs when food is made available to obese[13] children, as well as to children with other conditions associated with reduced energy intake, such as anorectic[14] and malnourished[15] children.

Analysis of the relationship between weight reduction in children and height change requires consideration of two important facts about child height. First, obese children are overnourished, are taller than nonobese children,[16] reach their growth spurt sooner,[16] and mature sexually earlier than nonobese children.[17] However, while they may be taller during development than nonobese children, the heights of obese and nonobese adults do not differ.[18] One hypothesis for the similarity in final height for obese and nonobese adults given the differences in height during development is that as obese children approach adulthood, their growth rate decreases and the height of nonobese children catches up. Thus, given that the patterns of growth to reach adult height in obese children are different from the patterns of nonobese children, longitudinal studies may show slower actual growth and a decrease in height percentiles in obese compared with nonobese children as they approach adulthood. Second, child height should be corrected for parental height when child growth patterns are assessed.[19] Most analyses of the relationship between weight change and height attained assess changes in height without reference to, and not adjusted for, parent height.[11-13]

In a previous analysis of the relationship between height and weight changes during a 5-year period,[20] we showed that obese children were taller than expected, that midparent height was the best predictor of child height, and that after treatment obese children had elevated height percentiles compared with their parents for most parent height categories. This report is designed to provide an analysis of factors that may influence height attained over a 5-year period in a large sample of children treated in controlled clinical trials in the Childhood Weight Control Program at the University of Pittsburgh (Pa) School of Medicine.

SUBJECTS AND METHODS

Subjects are children treated in one of four controlled outcome studies who have completed 5-year follow-up. Growth results from only one of these studies have been reported previously.[20] Subjects were between 6 and 12 years of age at entry, and between 20% to 100% above ideal weight for height, age, and sex.[21] Exclusion criteria include illiteracy, concurrent psychiatric diagnosis, unwillingness of at least one parent to participate in all treatment meetings, and for the exercise studies,[22,23] a medical problem that limits exercise. Demographic, height, and weight characteristics of the sample at baseline and after 5 years are given in Table 1. The inclusion of a variety of treatment and control conditions resulted in considerable variance in the effectiveness of treatment, with a range of outcome over 5 years from a decrease in percent overweight of −54.5% to an increase of +60.6%. The average child was slightly less obese after 5 years than before beginning treatment (percent overweight ± SD, −3.2% ± 20.8%), and 21% of the sample was not obese at follow-up. A

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From the Western Psychiatric Institute and Clinic, University of Pittsburgh (Pa) School of Medicine.

Reprint requests to the Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (Dr Epstein).

Table 1.—Demographic, Height, and Weight Data at Baseline and Over 5 Years (Mean ± SD)*

	Baseline	Change From 0-5 y
No. (M/F)	162 (47/115)	. . .
Age, y	10.38 ± 1.56	. . .
Height, cm	145.86 ± 11.35	20.29 ± 8.01
Height percentile	73.87 ± 22.71	−8.67 ± 20.69
Weight, kg	55.00 ± 12.82	24.58 ± 14.37
% overweight	44.72 ± 15.49	−3.20 ± 20.82
Parent midheight, cm	169.84 ± 5.44	. . .
Standardized physical maturity	2.47 ± 1.58	. . .

*Height percentiles are adjusted for parental height.

complete analysis of comparative effects of treatment and control groups over 5 years in these studies is presented separately.[24]

At baseline, children were at the 74th percentile for height and were almost 2.5 SDs above the mean in noninvasive measures of physical maturity.[25] The average socioeconomic status for the total sample was 43.3 ± 13.0, within the range of social strata IV represented by owners of medium-sized businesses, minor professionals, and technical workers (A. B. Hollingshead, unpublished data, 1975). The average family size was 1.7 ± 1.4 siblings. In the four studies previously mentioned, 187 families were initially randomized, and complete child and parental height and weight data at 5 years were available for 162 children, 86.6% of the total sample.

Characteristics of Treatment

The specific methods for each study have been described previously.[20,22,23,26] Several characteristics were common to each study. Weekly treatment meetings lasted from 8 to 12 weeks with active treatment continuing from 6 to 12 months. The primary method for reducing energy intake involved the traffic light diet,[27] a 3780- to 5040-kJ balanced diet that children were provided during the first 6 months of active treatment. Children remained on the diet while they were attempting to lose weight. When children lost enough weight to come within 10% of their ideal weight, they were instructed to gradually increase energy intake by 840 kJ/d to ensure maintenance of their weight. They were to continue this increase until they began to gain weight, when their energy intake was stabilized.

Measurements

At 5 years, participants were contacted and follow-up data were collected in one of three ways. First, families who remained close to Pittsburgh were measured in our laboratories using a balance beam scale and a laboratory-constructed height board calibrated to approximately 0.3 cm. Second, for families who had moved or who were unable to attend the follow-up, physician or nurse reports were used. Third, some additional families were allowed to provide self-reported heights and weights, which were adjusted to compensate for self-report bias using a regression equation derived from a database that compared measured and estimated height and weight for 313 subjects in our follow-up studies. Seventy-two percent of the 5-year sample were directly measured in our laboratory or by a physician or nurse. Families were paid for follow-up on a sliding scale, ranging from $100 for both parents and children coming to the laboratory for direct measurement, to $50 for nurse or physician reports, to $5 for self-reports.

Child height and weight data were converted to percent overweight using World Health Organization (WHO) weight for height percentiles,[21] expressed in terms of percentage over average weight for age, height, and sex. The WHO data were used rather than the National Center for Health Statistics (NCHS) growth data,[28] since the WHO data provide more extended weight for height data needed for percent overweight calculations. Many of the obese children in our sample are taller than the normative data provided in the NCHS growth data, and thus their percent overweight cannot be calculated. To ensure comparability of the NCHS and WHO standards, we compared average weights for male and female children at the extremes and midpoint of the NCHS sample with WHO average weight for the same heights. Pearson Product-Moment Correlation Coefficients for average weights for heights for the boys and girls across the two samples both exceeded $r = .99$, with a difference of only 0.13 kg in average weights for the heights and weights sampled across the two methods. The NCHS growth data[28] were used to calculate height percentiles, adjusted for parental height.[29] Physical maturity was estimated using noninvasive procedures based on the methods suggested by Roche et al,[25] which derive standardized physical maturity scores based on child recumbent length, weight, parent midstature, and age.

Analytic Procedures

Linear regression methods were used to model the influence of sex, age, weight, physical maturity, and parent midheight on baseline height (centimeter) and height percentile. Changes in height and height percentile over 5 years were modeled using the above variables in addition to changes in weight. The first step in the modeling was to examine the univariate correlation coefficients to assess which of the predictor variables were related to the dependent variables and should be put in the model. In addition, the univariate correlations were examined to assess variables that were intercorrelated to reduce any problems with multicolinearity. Backward regression procedures were used with the complete set of predictor variables including predictor variables that were significantly related to the outcome but that were generally unrelated to each other, and terms that did not meet significance were dropped in sequential fashion. Constants were included only if they added significantly to the model. Models were checked for multicolinearity and residuals were plotted against the estimates.

For purposes of graphic presentation, the distribution of parental height was broken down into tertiles, and the lowest tertile was arbitrarily labeled as short, the middle tertile was labeled as medium, and the highest tertile was labeled as tall. Based on parent midheight norms in comparison with adult height norms,[30] the average parent midheight norms for parents labeled as short were at the 18th percentile, average-height parents were at the 59th percentile, and tall parents were at the 91st percentile. Child height was not normally distributed, but it was positively skewed to the right, and it was divided into two groups at the 75th percentile for child height. This was approximately the mean for baseline child height percentiles.

RESULTS

Pearson Product-Moment Correlation Coefficients between the predictor variables and baseline and changes in height and height percentile are shown in Table 2. The regression models used to predict unadjusted baseline height and baseline height percentiles adjusted for parental height are shown in Table 3, while the models used to estimate change in these variables over time are shown in Table 4. While our major inter-

Table 2.—Pearson Product-Moment Correlations Between Child Height and Child Height Change and Child and Parent Demographic Variables*

	Age	Wt	Wt0-5	Mid	Mat	Ht0	Ht%0	Ht0-5	Ht%0-5
Sex	−.03	−.09	−.37†	−.01	−.21†	−.01	.04	−.43†	−.07
Age		.72†	−.29†	.03	−.29†	.80†	−.12	−.59†	.13
Weight			−.18‡	.13	.27†	.87†	.36†	−.54†	.02
Weight 0-5				.14	.13	−.20†	.04	.57†	.14
Midparent height					−.07	.29†	.07	.13	.20
Mature						.12	.65†	.13	−.10
Height 0							.39†	−.56†	.08
Ht%0								−.08	−.31†
Height 0-5									.35†

*Note Ht%0 is baseline height percentile adjusted for parental height; Ht%0-5, change in height percentile adjusted for parental height. Wt is baseline weight; Wt0-5, weight change; Mid, parent midheight; Mat, estimated physical maturity, and Ht0-5, height change.

†$P<.01$.

‡$P<.05$.

Table 3.—Regression Models Used to Predict Baseline Height and Adjusted Height Percentile

Variable	Coefficient	SE	t	P
Baseline height*				
Baseline weight	.76	0.033	23.03	<.001
Midparent height	.61	0.011	56.40	<.001
Baseline adjusted height percentile†				
Constant	35.23	6.00	5.88	<.001
Physical maturity	8.94	0.88	10.14	<.001
Weight	.30	0.11	2.72	<.001

*Multiple $r=.88$, adjusted $r^2=.79$, F(1,157) = 582.34, $P<.001$.

†Multiple $r=.68$, adjusted $r^2=.45$, F(2,156) = 66.65, $P<.001$.

Table 4.—Regression Models Used to Predict Change in Height and Standardized Adjusted Height

Variable	Coefficient	SE	t	P
Height change*				
Constant	58.27	2.96	19.70	<.001
Sex	−8.13	0.97	8.36	<.001
Age	−3.09	0.27	11.37	<.001
Change in adjusted standardized height†				
Baseline adjusted height	−.30	0.07	4.32	<.001
Midparent height	.08	0.03	2.51	.013

*Multiple $r=.74$, adjusted $r^2=.54$, F(2,159) = 96.38, $P<.001$.

†Multiple $r=.32$, adjusted $r^2=.10$, F(1,154) = 17.71, $P<.001$.

est was in the adjusted height percentile models, the unadjusted models are presented for comparison with other studies.

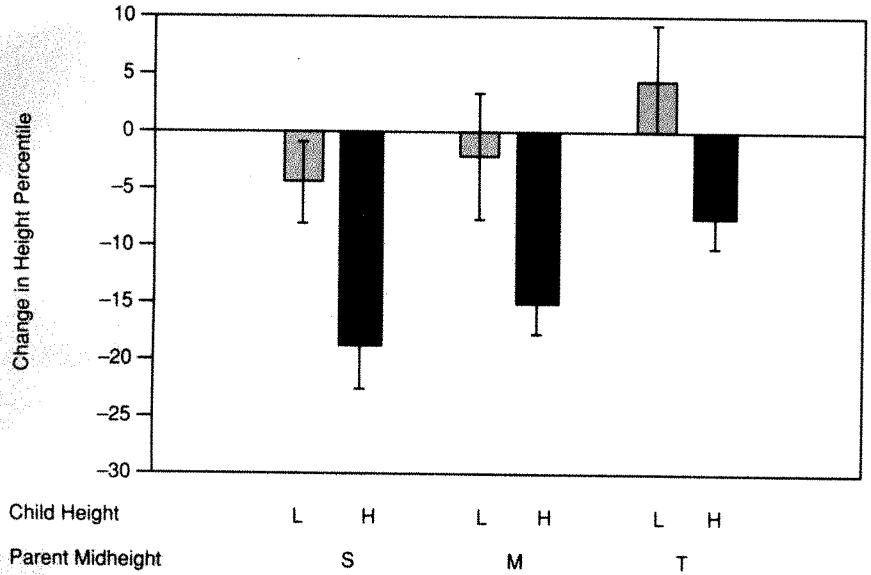
Initial height was related to age, weight, and midparent height, with age and weight being strongly related ($r=.72$) and multicollinear in prediction of initial height. The best fitting model for predicting initial height included two variables, weight and midparent height, accounting for 79% of the variance. Examination of the coefficients suggests that children with taller parents who are heavier were the tallest children at entry. Height percentile was related to initial weight and maturity. The model for height percentile accounts for 46% of the variance. Heavier children with greater physical maturity had the greatest height percentile.

Height change was related to sex, age, initial height, and weight change. Age was strongly related to initial height ($r=.80$), and the best fitting model included age in combination with sex, accounting for about half of the variance in absolute height change. Young boys who were relatively short at entry grew the most. Changes in height percentile were related to initial height and midparent height, with the model including these two parameters accounting for 9% of the variance. Weight change was not significantly related to changes in height percentile, and when added to the model, the percent of variance accounted for decreased to 8%. Children who were relatively shorter, with taller parents, showed the largest changes in height.

The interactive effects of child height and parental height on growth are shown in the Figure. Numbers above the line refer to increases in height percentile, while numbers below the line mean height percentile has decreased. As this figure shows, for each parental height grouping, child height exerts an effect: the taller the children, the more the decrease in height percentile. Children who were below the mean (L) in height percentile with tall parents showed a gain in relative height. Conversely, children above the mean (H) with short parents showed the greatest decrease in height percentile over 5 years.

ANALYSIS OF NONOBESE VS OBESE CHILDREN

To provide further documentation that changes in percent overweight were unrelated to outcome, *t* tests comparing age, sex, initial height, height change, initial height percentile, and changes in height percentile were run, comparing children who were not obese at 5 years with children who were obese. These two groups were marked by large differences in changes in percent overweight, as children who were nonobese at 5 years showed an average decrease of −23.04 ± 13.9 (mean ± SD) in percent overweight, while those who were obese at 5 years showed a slight increase of 2.1 ± 19.1 in percent overweight ($t[157]=3.28$, $P=.001$). However, even when the children who became



Change in child height percentile (mean ± SEM) over 5 years adjusted for parental height as a function of both child height and parental height. L indicates children below the mean; H, children above the mean; S, short; M, medium; and T, tall.

nonobese or remained obese were compared, no significant differences were observed for any of the height variables. The initial height percentile (mean ± SD) for children who became nonobese was 75.4 ± 24.8, which was not significantly different from that of children who were obese at the end of 5 years, 74.5 ± 21.3 ($t[157] = 0.26$, $P = .79$). Children who became nonobese (who showed the largest changes in percent overweight) had a slightly lower decrease in height percentile (−7.0 ± 21.3) than children who were obese at 5 years (−9.1 ± 20.6, $t[157] = 0.53$, $P = .60$).

COMMENT

This study shows that when changes in height percentile over 5 years are adjusted for parental height, two variables are predictive of the change over 5 years: child initial height percentile and parent height. Child weight change makes no additional contribution to understanding changes in child height percentile. When absolute height is considered, child age and sex make contributions to changes in height over 5 years.

Height of children in this sample remained relatively elevated compared with population normative data even after a decrease in height percentiles. At baseline the average obese child in our sample was at the 74th percentile for adjusted height, and after 5 years the average obese child was at the 65th percentile. These results are consistent with several other reports showing that obese children are taller than their nonobese peers.[13,16] Thus, assuming the final height of these children will be similar to the height of nonobese children, these obese children could show considerably slower changes in height than nonobese children during late adolescence and reach heights similar to nonobese children.

The effects of parental height on child growth over 5 years are consistent with other reports that suggest parental height is important in determining child growth and final height.[17,19,20] Most analyses of the relationship between weight change and height assess changes in height without standardization for parental height and without consideration that child height percentiles should be referenced to parent height.[11-13] In this study the children who showed the most growth were those who were relatively short at baseline but who had tall parents, while the children who grew the least were those who were relatively tall at baseline but had short parents. These patterns would be expected in children independent of whether they had participated in programs to treat obesity. It is important when advising parents that pediatricians acknowledge both child and parental height in projecting growth. Tall children with short parents would not be expected to grow as fast as children who are shorter with taller parents.

While these results are encouraging to investigators and practitioners interested in treating obese children, it is important not to overgeneralize these results to other treatments and children of other ages. The present results assessed growth for a sample of predominantly female children who began treatment during a variety of developmental stages. Physical maturity, which our data suggest is important in predicting initial standardized height but not change in standardized height, was not measured directly but was assessed using regression equations based on noninvasive measures.[27] While in our sample changes in height percentiles were unrelated to age or sex, further research on larger samples that control level of maturation would be important to increase confidence in the generality of these findings. In addition, it may be that treatments that do not emphasize energy regulation and do not promote a balanced diet may cause problems in growth. Likewise, treatment of younger children at different stages of development may be harmful. It is advisable to be cautious in modifying diets of growing children to ensure adequate nutrition. Child height should be regularly monitored, taking into account both parent height and the position of a child's height in relationship to his or her peers.

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Asymptomatic Congenital Cytomegalovirus Infection

Audiologic, Neuroradiologic, and Neurodevelopmental Abnormalities During the First Year

W. Daniel Williamson, MD; Alan K. Percy, MD; Martha D. Yow, MD; Paul Gerson, MD;
Francis I. Catlin, MD; Mark L. Koppelman, MA†; Susan Thurber

• Twenty-eight infants with asymptomatic congenital cytomegalovirus infection and 13 control infants were followed up prospectively. Congenital sensorineural hearing loss was documented by auditory brain-stem responses in four infected infants (two had mild bilateral loss, one had mild unilateral loss, and one had extreme unilateral loss) but in no controls. Four infected infants had diffuse periventricular radiolucencies on computed tomographic scan; none had calcifications or ventriculomegaly. No differences between groups were noted on neurologic examination results or on the Bayley Mental Developmental Index; however, one infected infant had a severely delayed Bayley Psychomotor Developmental Index score. In addition, the mean Mental Developmental Index score of the four infected infants with diffuse periventricular radiolucencies was significantly below that of the remaining infected infants (93 ± 8 vs 109 ± 13). These data suggest that asymptomatic congenital cytomegalovirus infection may be associated with a broad range of audiologic, subtle neuroradiologic, and neurodevelopmental differences in early infancy.

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Although cytomegalovirus (CMV) is the most frequent cause of congenital infection in man, the majority of infected infants lack clinical signs at birth and are identified only through screening programs.[1] Currently, data about the developmental, neurologic, and audiologic status of these initially asymptomatic infants suggest widely varying outcomes.[2-9] Although sensorineural hearing loss has been documented in older asymptomatic children, the frequency of congenital abnormalities diagnosed by auditory brain-stem responses (ABRs) of asymptomatic infants has not been determined.[2-9] In addition, neuroradiologic studies of asymptomatic infants are lacking.

The purpose of this study was to establish the prevalence of congenital sensorineural hearing loss in 28 infants with asymptomatic congenital CMV infection compared with uninfected controls, and to investigate the role of computed tomography (CT) in the identification of asymptomatic infants at risk for early neurodevelopmental delay.

PATIENTS AND METHODS

Patients

Twenty-eight congenitally infected infants were enrolled in the first phase of a prospective longitudinal study carried out at the Meyer Center for Developmental Pediatrics, Texas Children's Hospital, and Baylor College of Medicine, Houston. Parents of an additional four infants could not commit to the time required for the project. Twenty-six of the 28 infected infants were born at a private maternity hospital that routinely performs neonatal urine cultures for CMV, as previously described.[10] Ten of the 26 infants were born to mothers who had primary CMV infections during pregnancy, as documented by seroconversion; four infants were born to mothers who were IgG positive and IgM negative during the first 12 weeks of pregnancy and therefore presumed to have recurrent CMV infections. The status of the other 12 mothers could not be determined. Neonatal CMV cultures were performed on the remaining two infected infants, born at outlying private hospitals, because their mothers had symptomatic primary CMV infections documented during pregnancy. None of the 28 infants had petechiae, hepatosplenomegaly, microcephaly, direct hyperbilirubinemia, or chorioretinitis. Twenty-seven infants had birth weights appropriate for gestational age; one infant whose birth weight was just below the fifth percentile was the smaller of infected twins. Thirteen infants who had negative CMV urine cultures were selected as controls; review of their records revealed normal Apgar scores, no evidence of perinatal distress, and normal results of newborn examinations. No attempt was made to match for socioeconomic status since all infants were born at private hospitals.

Infected infants and control group infants did not differ significantly in birth weight (3336 ± 608 g vs 3385 ± 633 g [mean ± SD]), gestational age (39 ± 1.6 weeks vs 40 ± 2.4 weeks), race (89% white and 11% black vs 85% white and 15% black), sex (39% male and 61% female vs 31% male and 69% female), or socioeconomic status by Hollingshead classification (43% higher socioeconomic status [groups 1 and 2] vs 54% higher socioeconomic status).[11]

Methods

The study protocol was approved by the Institutional Review Boards of both Texas Children's Hospital and Baylor College of Medicine. All 41 infants during the first 4 months of life had ABRs that were recorded

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From the Departments of Pediatrics (Drs Williamson, Percy, and Yow, and Ms Thurber) and Otolaryngology (Dr Catlin), Baylor College of Medicine, Houston, Tex, and the Meyer Center for Developmental Pediatrics (Dr Williamson and Ms Thurber), the Department of Otolaryngology and Audiology (Dr Catlin and Mr Koppelman), and the Department of Neuroradiology (Dr Gerson), Texas Children's Hospital, Houston.

†Deceased.

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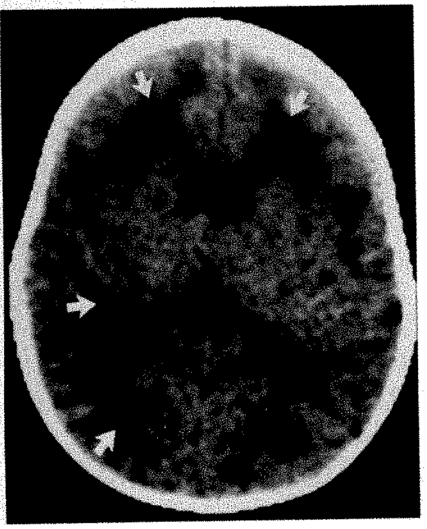
to alternating clicks at a duration of 0.15 milliseconds to each ear via TDH39 headphones (Telephonics Corp, Huntington, NY) at intensities of 20, 40, 60, and 80 dB. The intensity series was at a rate of 21 clicks per second. Measurements were made of wave I and wave V latencies and of the I-V interwave interval; they were compared with standards published by Salamy and McKean.[12] The ABR was performed by a single audiologist unaware of the group status (infected vs control). If abnormalities were detected on ABR, ABR was repeated and tympanometry performed to exclude middle ear disorder as a cause of the hearing loss. Behavioral audiometry was not performed during the first year. Abnormal responses were rated as follows: slight, responses at 25 to 40 dB; mild, 40 to 55 dB; moderate, 55 to 90 dB; and extreme, more than 90 dB.[13]

Unenhanced cranial CT scanning was performed on infected infants at a mean age of 6±3 weeks (8800 model, General Electric, Milwaukee, Wis). Computed tomographic scans were reviewed independently by a pediatric neuroradiologist and a pediatric neurologist who were unaware of the infants' developmental and neurologic status. Computed tomographic scans were reviewed for the presence of calcifications and for ventricular size based on lateral ventricular ratio (maximum width of the body of the lateral ventricle divided by half the biparietal diameter). In addition, brain substance density ratings calculated according to Schrumpf et al[14] were as follows: (1) no low-density zones, (2) cortical low-density zones, (3) mild periventricular low-density zones immediately adjacent to frontal and occipital horns, or (4) moderate to severe low-density extending from zones contiguous with the frontal and occipital horns, around the bodies of the lateral ventricles into the centrum ovale, and to the gray matter/white matter border.

Moderate to severe periventricular radiolucencies in an infant with asymptomatic congenital cytomegalovirus infection.



A standard neurologic examination, performed between ages 4 and 9 months by a pediatric neurologist unaware of group status, was rated as follows: (1) normal rating indicated normal or questionable tone or reflexes; (2) mildly abnormal, definite hypertonia or hypotonia not affecting performance; and (3) severely abnormal, definite hypertonia or hypotonia affecting performance.

Developmental assessment on the Bayley Scales of Infant Development was performed on all subjects at an average age of 10±2 months by a trained physical therapist unaware of patient groups.[15] While not necessarily predictive of future performance, the Bayley Scales yield information regarding the infant's current level of function compared with normative data. The Bayley Scale has both a Mental Developmental Index (MDI) and a Psychomotor Developmental Index (PDI) with means of 100 and SDs of 16. The MDI and PDI scores were categorized as the following: (1) normal, 84; (2) mild delay, 68 to 84; (3) severe delay, less than 68.

Differences between groups were analyzed by Student's *t* test or χ^2 and further assessed by multiple regression analyses.[16]

RESULTS

All 13 control infants had normal audiologic assessments. However, four of 28 infected infants had congenital sensorineural hearing loss: two had mild bilateral loss, one had mild unilateral loss, and one had extreme unilateral loss. On CT scan, all 27 infected infants scanned had normal ventricular size and no evidence of calcifications. Four infants had evidence of moderate to severe periventricular diffuse radiolucencies that extended from zones contiguous with the frontal and occipital horns around the bodies of the lateral ventricles (Figure).

No significant differences in neurologic status between the infected infants and the controls were noted. The mean Bayley MDI and PDI did not significantly differ between the control group and the infected group of 24 infants who returned for developmental assessment (Table). However, one infected infant with a normal CT scan, ABR, and MDI had a severely delayed PDI; none of the control infants were severely delayed.

Multiple regression procedures were used to investigate the relationship between CT scan findings, other indepen-

Developmental and Neurologic Status at Age 10 Months of Infants With Asymptomatic Congenital Cytomegalovirus Infections and Control Infants

		Infected Infants†					
	Controls* (n=13)	Total (n=24)	Normal CT Scan (n=20)	Abnormal CT Scan (n=4)	Primary Maternal Infection (n=10)#	Reactive Maternal Infection (n=4)#	Unknown Maternal Infection (n=10)#
MDI (mean ± SD)	107±15‡	**107±14‡**	109±13‖	93±8‖	109±14	98±9	109±16
PDI (mean ± SD)	101±15§	**100±15§**	102±15¶	92±18¶	97±18	106±12	102±13
MDI, No.							
Normal	12	**23**	20	3	9	4	10
Mild delay	1	**1**	0	1	1	0	0
Severe delay	0	**0**	0	0	0	0	0
PDI, No.							
Normal	11	**22**	19	3	8	4	10
Mild delay	2	**1**	0	1	1	0	0
Severe delay	0	**1**	1	0	1	0	0
Neurologic status, No.							
Normal	12 (92%)	**23** (96%)	20	3	10	4	9
Mildly abnormal	1 (8%)	**1** (4%)	0	1	0	0	1
Severely abnormal	0	**0**	0	0	0	0	0

*MDI indicates Mental Developmental Index; and PDI, Psychomotor Developmental Index.
†CT indicates computed tomographic.
‡$t = .02$, $P > .05$.
§$t = .19$, $P > .05$.
‖$t = 3.23$, $P < .05$.
¶$t = .99$, $P > .05$.
#No significant difference between the three groups (primary, reactivation, and unknown).

dent variables (eg, socioeconomic status, sex, and birth weight) and developmental performance of the infected group. The best prediction of developmental performance for this group was achieved with two independent variables: CT scan abnormalities and socioeconomic status. Together, these variables explained 25% of performance variance ($R^2 = .5$). Of these two variables, CT abnormality independently explained a significant portion of the developmental performance variance (β coefficient = 17.4, t ratio = −2.56, $df = 23$, two-tailed $P < .02$); however, socioeconomic status failed to achieve significant levels (β coefficient = −3.63, t ratio = −1.88, $df = 23$, two-tailed $P < .10$). A significant difference in the Bayley Scale MDI was found between those four infants with moderate to severe periventricular radiolucencies and the remainder of the infected group (Table); no significant difference in the PDI was found, perhaps because of the large range of scores for the four infants with radiolucencies.

Meaningful analysis of the relationship between infant outcome and maternal seroimmunity was limited because of small group size and because the serologic status of 12 of 28 mothers was unknown (Table). However, all four patients with congenital hearing loss were born to mothers who experienced primary CMV infections during pregnancy, as was the case with severely delayed PDI. In addition, the mothers of three of the four infected patients with periventricular radiolucencies on CT scan had primary infections, but the mother of the fourth had CMV reactivation during pregnancy.

COMMENT

The frequency of congenital CMV, estimated to have occurred in 38 000 births in the United States in 1987 alone, raises critical public health issues about the impact of this intrauterine infection.[17] The deleterious effects of congenital CMV on the developmental, neurologic, and audiologic function of infants who are symptomatic at birth have been clearly documented.[18-19] However, the exact impact of the prenatally acquired disease for the much larger, asymptomatic group is less clearly defined.

Reports from the United States, Canada, and Great Britain regarding the outcome of the asymptomatic group are, at times, conflicting and confusing.[2-8] Some investigators found children with asymptomatic congenital CMV infection to be at greater risk for school problems.[2,3] Others found no differences in developmental performance of infected and control groups.[4-8] However, several studies reported individual infants with asymptomatic congenital CMV infection who later were significantly impaired.[2,4] Also, sensorineural hearing loss in the infected children tested at preschool age or later was noted.[2-6,8] The conflicting findings of these studies and the documentation that individual asymptomatic infants may have severe abnormalities on follow-up led to the establishment of the this study.

In this study, congenital sensorineural hearing loss occurred in 14% of the asymptomatic infected infants, a rate slightly less than in several preceding studies. Severe to profound *bilateral* loss was not found in this study group, but has been noted in other studies.[2,4] While this discrepancy may be by chance, another possible explanation is that previous studies tested infected children at older ages rather than during infancy; thus, undocumented deterioration in audiologic function may have occurred prior to testing. Follow-up of this study population will allow this issue to be addressed definitively.

Although unenhanced CT scanning was not beneficial in the early identification of the one infected infant with significant psychomotor delay, diffuse periventricular radiolucencies that extend to the gray matter/white matter junction were significantly related to early developmental performance as assessed by the Bayley Scale MDI. The importance of periventricular radiolucencies on CT scans of other high-risk infants, particularly premature infants, is debated.[20-22] However, diffuse radiolucencies extending from the periventricular area to the gray matter/white matter junction are reportedly associated with poorer early developmental performance of term infants.[14,23,24] The relationship of early periventricular radiolucencies to long-term neurodevelopmental status of infants with asymptomatic congenital CMV infections will require further study.

The neuropathologic equivalent to diffuse radiolucencies on CT scan is not well documented. These low-density areas may represent cellular immaturity, hypomyelination, or increased water content, or may correspond to ischemic or infarcted areas when they occur in asphyxiated or otherwise compromised infants.[25] However, varying degrees of correlation between these neuroradiologic abnormalities and neuropathologic lesions have been described.[26,27] Although no studies have correlated findings of CT scans with those of the neuropathologic characteristics of congenital CMV, Post et al[28] have reported comparative studies in adults with acquired immunodeficiency syndrome who have acquired CMV encephalitis at the time of death. Results of CT scanning showed that several patients had diffuse white-matter hypodensities; however, neuropathologic studies revealed those abnormalities to be much more widespread than suspected based on the CT scan findings. The investigators concluded that CT scans were relatively insensitive for detecting the extent of CMV encephalitis. The use of magnetic resonance imaging may be more sensitive in future investigations.

The pathophysiology of the most frequent neuropathologic abnormalities noted in symptomatic congenital CMV (periventricular necrosis, calcifications, and microgyria) is most often thought to be direct tissue invasion by the virus. Recently, Marques Dias et al[29] have proposed a different explanation. Noting that these lesions are similar to those attributed to ischemia, as described by Banker and Larroche,[30] they hypothesize that perfusion failure may be a major event causing the neuropathologic lesions in symptomatic congenital CMV. Thus far, there are no neural tissue studies of infants with asymptomatic congenital CMV to correlate with the CT scan findings noted in the present study. Clearly, further investigation is needed to explore the pathophysiology and neuropathology of asymptomatic congenital CMV infection in order to explain clinical outcome.

Finally, an issue potentially related to outcome of congenital CMV infection is maternal seroimmunity. In this study

75% of those with known maternal status were born after primary maternal CMV infections, a reflection of the middle and upper-middle class distribution of the sample. These sampling characteristics differ greatly from the other US samples studied, who were largely of lower socioeconomic status and, thus, likely to be born following recurrent maternal CMV infection.[6,7,31] Such differences may relate to outcome variability and must be investigated further with a larger sample size.

The terms *ubiquitous* and *protean* were used by Weller[32] in 1971 to describe the ever-present nature and widely varying effects of CMV. These basic characteristics of CMV must be remembered as explanations are sought for differences in outcome data from this and previous studies. Efforts must be broadened to search for explanations by increasing well-defined study sample sizes, using standard assessment batteries and the most widely accepted terminology, and including maternal serologic status when possible. Since an estimated 5000 to 6000 infants born annually with asymptomatic congenital CMV infections apparently have early audiologic, neurologic, or developmental problems, it is imperative that such techniques be used by multiple centers to fully explore the public health issues related to congenital CMV infection.

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Diagnostic Aspects and Syndromal Associations of Short Trachea With Bronchial Intubation

Theadis R. Wells, HT(ASCP); Alma L. Wells, MD; Daniel A. Galvis; Melvin O. Senac, Jr, MD;
Benjamin H. Landing, MD; Linda A. Vachon, MD

• Conditions with disproportionately short trachea, with a reduced number of tracheal cartilage rings and a high level of tracheal bifurcation, have been reported. We have seen accidental bronchial intubation in nine patients with short trachea. This risk can be reduced by recognition of conditions associated with short trachea, by awareness that methods for calculating endotracheal tube length from body length can overpredict tube length for patients with short trachea, and, when feasible, by use of preintubation chest roentgenograms showing air bronchograms to establish the thoracic level of tracheal bifurcation. Twelve patients with short trachea, four with bronchial intubation, and six conditions not previously associated with short trachea, are reported. Three of the patients also had laryngeal hypoplasia.

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Reported hazards of tracheal intubation in neonates and infants include bronchial intubation.[1-7] Jones and Pelton[8] listed 25 syndromes with brevicollis (short neck) as a feature but did not specify a relationship of short neck to short trachea. Landing and Dixon[9] reported disproportionately short trachea due to a reduced number of tracheal cartilage rings in a patient with brevicollis, high tracheal bifurcation has been demonstrated roentgenographically in a patient with laryngotracheoesophageal cleft,[10] and Sein et al[11] have reported a high incidence of short trachea in patients with DiGeorge anomaly.

Wells et al[12,13] have recently reported several syndromal associations of "short trachea," as shown by a roentgenographically demonstrable high thoracic level of tracheal bifurcation (at vertebra T-3 or above vs normal at T-4 up to 2 years of age, or at T-4 or above vs normal at T-5 at greater than 2 years of age), a reduced number of tracheal cartilage rings (from a normal of 17 to 15 or fewer), or both. In those studies, accidental bronchial intubation occurred in neonates and infants with short trachea, with sequelae such as ipsilateral pulmonary emphysema and contralateral atelectasis.

The purposes of this study were to present additional conditions with which short trachea can be associated and additional instances of bronchial intubation in patients with short trachea.

MATERIALS AND METHODS

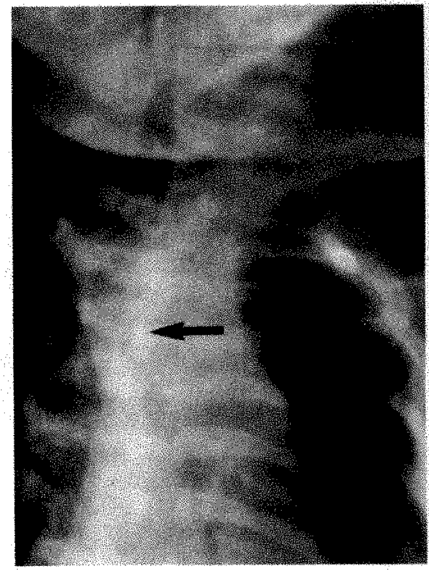
We performed a review of antemortem anteroposterior chest roentgenograms with demonstrable air bronchograms from the teaching file of the Department of Radiology, Childrens Hospital of Los Angeles (Calif). In addition, for a 6-month period, assessable anteroposterior chest roentgenograms of neonates, infants, and children from the neonatology and pediatric intensive care units of Childrens Hospital of Los Angeles and from the Shriners Hospital for Crippled Children, Los Angeles, were evaluated for a high thoracic level of tracheal bifurcation, as were chest roentgenograms that were available for patients who were autopsied during the preceding 10 years. Chest roentgenograms of approximately 275 patients were evaluated by counting the thoracic vertebrae down to the 12th vertebra and then counting back up to the tracheal bifurcation.[12] Attention was given to the absence of ribs or the presence of extra ribs to ensure correct determination of the vertebral level of tracheal bifurcation, and roentgenograms that appeared to have been obtained with the patient's spine and mediastinum at an unusual angle (usually hyperlordotic) to the x-ray beam were not included in the study.

Tracheal ring counts were performed after dissection, staining with 0.25% toluidine blue at a pH level of 2, and clearing intact tracheas obtained at autopsy and fixed in 4% formaldehyde.

RESULTS

The normal level of tracheal bifurcation, as demonstrated roentgenographically, is at the fourth thoracic vertebra until 2 years of age and is at T-5 thereafter (Fig 1). Twelve patients with short trachea have been identified since our previous study,[12] by roentgenographic demonstration of a high thoracic level of tracheal bifurcation (nine patients), by a reduced number of tracheal cartilage rings (two patients), or by both (one patient) (Table). Seven of these patients had conditions not previously reported in association with short trachea: Nager's acrofacial dysostosis (two patients), CHILD syndrome (congenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efect) (one patient), Möbius sequence (one patient), partial chromosome 3 trisomy (one patient), generalized GM_1 gangliosidosis type 1 (one patient), and short rib–polydactyly syndrome (one patient). Patients in this study found to have conditions previously associated with short trachea included two with Jarcho-Levin syndrome (spondylothoracic dysplasia),

Fig 1.—Anteroposterior chest roentgenogram of a 4-month-old female infant with CHILD syndrome (congenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efect) (patient 5 in Table) showing tracheal bifurcation (arrow) at the T2-3 vertebral level, indicative of short trachea (see Fig 4). Normal carinal level at this age is at T-4.



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From the Departments of Pathology and Laboratory Medicine (Messrs T. Wells and Galvis and Dr Landing) and Radiology (Dr Senac), Childrens Hospital of Los Angeles (Calif); the Division of Anesthesiology, Shriners Hospital for Crippled Children, Los Angeles (Dr A. Wells); and the Department of Radiology, Los Angeles County General Hospital and the University of Southern California School of Medicine (Dr Vachon).

Reprint requests to the Anatomic Pathology Division, Box 103, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Mr T. Wells).

New Patients With Short Trachea, Not Described by Wells et al[12,13]

Patient	Diagnosis (Genetic Catalog No.[17])	Age at Study	Body Length, cm	No. of Tracheal Rings	Roentgenographic Level, Tracheal Bifurcation	Comments
1	Hypoplastic left heart complex (24155)	10 d	53	. . .	T-3	Had right bronchial intubation, with left lung atelectasis; died at age 10 d
2	Hypoplastic left heart complex	12 d	50.5	. . .	T-3	Had right bronchial intubation, with left lung atelectasis; died at age 12 d
3	Jarcho-Levin syndrome (spondylothoracic dysplasia, 22730)	27 d	. . .	. . .	T-3	Patient is alive
4	Jarcho-Levin syndrome	9 y	108	. . .	T3-4	Normal for age is T-5; patient is alive
5	CHILD syndrome (30805)*	4 mo	46	12.5	T-3	Had laryngeal hypoplasia; died at age 4 mo (Fig 4)
6	Jeune's syndrome, type 1 (asphyxiating thoracic dystrophy, 20850)	1 d	. . .	. . .	T-3	Had right main bronchial intubation, with right pneumothorax and left lung atelectasis; died at age 1 d
7	Möbius' sequence (15790)*	4 y	82.5	. . .	T3-4	Patient is alive; normal carinal level for age is T-5
8	Nager's acrofacial dysostosis (15440)*	20 wk gestation	23	12.5	. . .	Had laryngeal hypoplasia; died at age 1 d
9	Nager's acrofacial dysostosis*	36 wk gestation	41	15	. . .	Had laryngeal hypoplasia; died at age 12 d
10	Partial chromosome 3 trisomy*	1 d	43	. . .	T-3	Died at age 1 d
11	Generalized gangliosidosis, GM$_1$, type 1 (23050)*	6 mo	61	. . .	T-3	Died at age 6 mo
12	Short rib–polydactyly syndrome, non-Majewski type (26351, 26353)*	1 d	37	. . .	T-3	Had left bronchial intubation with pneumothorax (Fig 3); died at age 1 d

*Conditions for which association with short trachea have not been reported previously, to our knowledge.

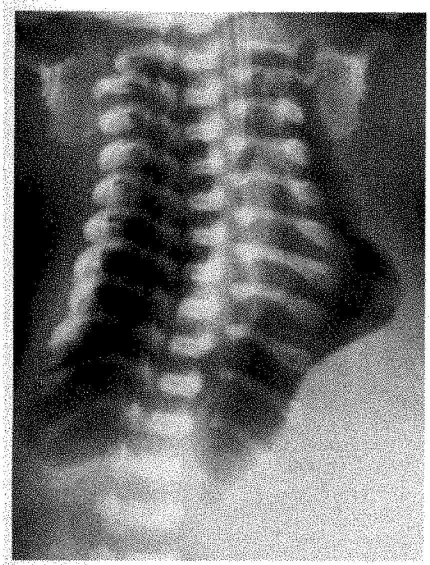

Fig 2.—Anteroposterior chest roentgenogram of a newborn infant with asphyxiating thoracic dystrophy type 1 showing the endotracheal tube extending approximately 8 mm into the right main bronchus, with associated right pneumothorax and left lung atelectasis.

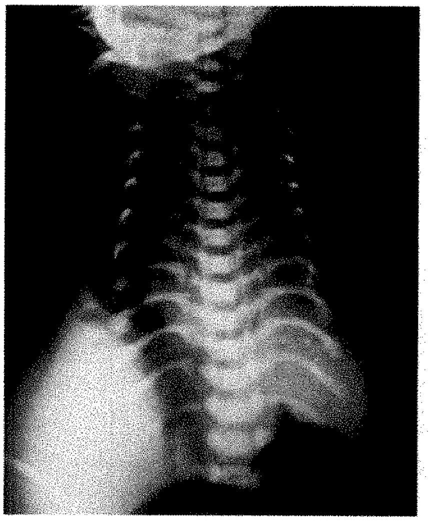

Fig 3.—Anteroposterior chest roentgenogram of a newborn male infant with non-Majewski short rib–polydactyly syndrome showing intubation of the left main bronchus with pneumothorax. The tracheal bifurcation is at T-3.

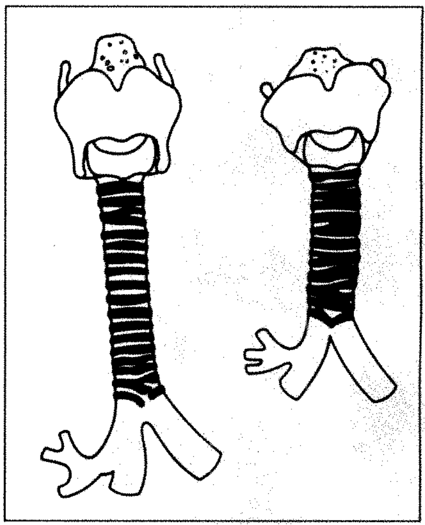

Fig 4.—Tracings from photographs of stained and cleared larynges and tracheas of a 1-month-old control patient (left) and a 4-month-old female infant with CHILD syndrome (congenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efects) (right) whose chest roentgenogram is shown in Fig 1, showing short trachea (with 12.5 cartilage rings vs normal, 17 ± 1 [mean ± SD]) and laryngeal hypoplasia. The roentgenographic level of tracheal bifurcation was T2-3.

one with Jeune's syndrome (asphyxiating thoracic dystrophy) type 1, and two with hypoplastic left heart complex.

Accidental right bronchial intubation was shown roentgenographically in three patients with short trachea, one with Jeune's syndrome, and two with hypoplastic left heart complex; left bronchial intubation was seen in the neonate with non-Majewski short rib–polydactyly. Figure 2 shows right lung emphysema and left lung atelectasis secondary to right bronchial intubation in the patient with Jeune's syndrome, and Fig 3 shows left bronchial intubation and pneumothorax in the neonate with short rib–polydactyly syndrome. Laryngeal hypoplasia was noted in three of the patients with short trachea, one with CHILD syndrome, and two with Nager's acrofacial dysostosis.

The tracings in Fig 4, made from photographs of stained, cleared tracheas, show 17 tracheal cartilage rings in a 1-month-old control infant compared with only 12.5 rings in the 4-month-old infant with CHILD syndrome whose tracheal bifurcation was at T2-3 on anteroposterior chest roentgenograms (Fig 1).

The general incidence of short trachea in the population of hospital patients without specific syndromes cannot be stated, as the thoracic level of tracheal bifurcation is often not visualizable in routine chest roentgenograms of infants and children.

COMMENT

Short trachea appears to contribute significantly to the group of infants and children whose major bronchi (usually right) are accidentally intubated.[12,14] Roentgenographically, this anomaly can be recognized by a high thoracic level of tracheal bifurcation, at vertebral level T-3 or above in neonates and infants or at T-4 or above in patients older than 2 years, when an adequate air bronchogram is visible (Fig 1), when the angle of the x-ray beam is appropriate, and when thoracic vertebral anomalies do not preclude the determination.

For patients with conditions associated with short trachea, preintubation chest roentgenograms obtained with a high-kilovolt technique can be helpful in the establishment of the level of tracheal bifurcation, by providing an assessable air bronchogram.

Short trachea is highly associated with a reduced number of tracheal cartilage rings to 15 or fewer vs normal, 17.03 ± 1.28 (mean ± SD).[12] Ten patients in the previous study and one in this study had short trachea demonstrated both by a high tracheal bifurcation seen on anteroposterior chest roentgenograms and by a reduction in the number of tracheal cartilage rings. One patient encountered in this study, a 19-month-old female infant with microcephaly, dysmorphic facies, and sepsis, had 14.5 tracheal cartilage rings (normal, 17.03 ± 1.28) but tracheal bifurcation at T4-5. This is the only patient encountered in this or in our previous study[12] who had fewer than 15 tracheal rings but a roentgenographically normal level of tracheal bifurcation.

Three patients in this study had both laryngeal hypoplasia and short trachea: the one with CHILD syndrome and those with Nager's acrofacial dysostosis. The association of laryngeal hypoplasia and short trachea has been reported for the DiGeorge anomaly,[11,15] but the frequency with which these two lesions are associated in other syndromes is not known. The requirement of a disproportionately small endotracheal tube size for the patient's age[16] can, however, raise the issue of short trachea.

Short trachea has been reported[10-13] in patients with laryngotracheoesophageal cleft; DiGeorge anomaly; interrupted aortic arch; hypoplastic left heart complex; congenital heart disease in patients without DeGeorge anomaly, interrupted aortic arch, or hypoplastic left heart complex; diaplacental rubella; brevicollis (including Klippel-Feil and Jarcho-Levin syndromes); osteogenesis imperfecta; Ellis–van Creveld syndrome; achondrogenesis type 2; Kniest syndrome; hypophosphatasia (spur-limbed dwarfism form); mesomelic dwarfism; Jeune's syndrome; and neural tube defect with myelomeningocele. In the present study, in addition to patients with hypoplastic left heart complex, Jarcho-Levin syndrome, and Jeune's syndrome, short trachea was found in patients with Nager's acrofacial dysostosis, CHILD syndrome, Möbius sequence, generalized GM_1 gangliosidosis type 1, partial chromosome 3 trisomy, and short rib–polydactyly syndrome. Patients with short trachea in whom we have observed accidental bronchial intubation to date include two each with hypoplastic left heart complex, DiGeorge anomaly and neural tube defect and one each with diaplacental rubella, Jeune's syndrome type 1, and short rib–polydactyly syndrome (non-Majewski type).

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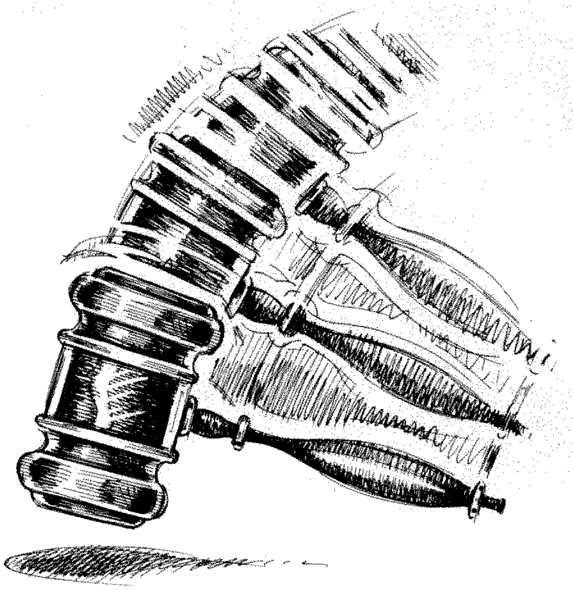
Doctor, Guilty or Innocent?



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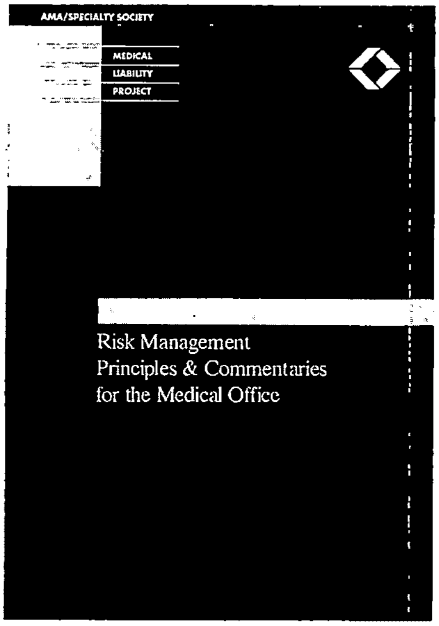

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THIRD PEDIATRICIAN — BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105, or (218) 829-4901. Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

TEXAS — BE/BC pediatrician to join busy, three-pediatrician group in Dallas/Fort Worth Metroplex. Competitive salary, incentives and benefits. Contact: Dan Geppert, MD, 950 North Davis, Arlington, TX 76012. (817) 460-0104.

ESTABLISHED two person practice experiencing explosive growth looking for BE/BC pediatrician. Located on the beautiful southern California coast, one hour north of Los Angeles. May begin anytime. For information contact: Mark Freedenberg, MD, 2793 Loma Vista Road, Ventura, CA 93003. (805) 656-3900.

PEDIATRICIAN — Board-certified/-eligible. Excellent opportunity for well-trained physician to join a 50-physician multi-specialty group in progressive, dynamic practice. Well-established, 5-physician department. Affiliate hospital recently underwent complete renovation and expansion. Competitive salary/comprehensive benefit package includes: malpractice insurance, flexible benefits plan, 401K and profit sharing, relocation assistance. Send CV: Olmsted Medical Group, Attention: Susan Schuett, 210 Ninth Street Southeast, Rochester, MN 55904.

PEDIATRICIAN to join busy, small group practice. Town of 100,000, one hour north of San Francisco. Call shared with other pediatricians. Guaranteed salary leading to partnership. Send CV to: Pediatrics, 990 Sonoma Avenue, #5, Santa Rosa, CA 95404.

PEDIATRICIAN with training in behavioral and/or developmental pediatrics. Part-time. Resident supervision of behavioral curriculum development in primary care pediatric training program. Call or write: Dr. Emalee Flaherty, MD, Columbus Hospital, 2520 Lakeview, Chicago, IL 60614. (312) 883-5908.

COLORADO — Exceptional opportunity for two BC/BE pediatricians for established practice with history of patient loyalty. Front Range, one hour from Denver, 50,000, three percent Medicaid, four percent bad debt, year round sports, outstanding family community lifestyle. Send inquiries with curriculum vitae to: Box #117, c/o ADJC. Include day or evening telephone number.

Professional Opportunities

OBERLIN, OHIO — Multi-specialty group seeks BC/BE pediatricians to serve growing patient load. Northern Ohio college town serving drawing area of 275,000. Salary, liberal benefits first year with full shareholder status available thereafter. Send CV to: Dr. VanDyke, 224 West Lorain, Oberlin, OH 44074.

COLORADO — BC/BE pediatrician to join seven-pediatrician department of established, multi-specialty clinic. Contact: Jos. L. Corrigan, MD, 209 South Nevada Avenue, Colorado Springs, CO 80903. (719) 475-7700.

PHILADELPHIA AREA: Three pediatricians seeking BE/BC fourth in a growing suburban community. One office, minutes from hospital. Full partnership opportunity after two years. Convenient access to Philadelphia; recreational opportunities in nearby Pocono Mountains, and/or New Jersey beaches. Reply to: Box #115, c/o AJDC.

NEWPORT, VERMONT: Board-certified, solo practitioner seeks BE/BC associate to join a rapidly growing solo practice, early partnership possible. Beautiful, rural, northern Vermont. Challenging patient load. Good university affiliations. Reply: T.A.E. Moseley, MD, North Country Hospital, Newport, VT 05855.

THREE PEDIATRICIANS in a multi-specialty group of sixteen physicians seeking a fourth pediatrician to join our extremely busy and well-established practice in a city in Texas of 94,000 with a drawing area of approximately 250,000. Our city offers many cultural activities, as well as a four-year state supported university. Attractive benefit package, guaranteed salary, and the opportunity to join our partnership. For further information, please contact: Dr. Kenneth Sultemeier at (817) 723-1411. Or mail your CV to: The Medical and Surgical Clinic, 1518 Tenth Street, Wichita Falls, TX 76301.

THE DEPARTMENT OF PEDIATRICS, Medical College of Wisconsin is expanding its general pediatrics section. We are creating a general pediatric inpatient service of two physicians and adding two physicians to our outpatient service. The section currently has seven physicians who provide outpatient care for more than 6,000 children and adolescents, inpatient coverage at Children's Hospital of Wisconsin, teach medical college medical students, and 41 pediatric residents. Interested pediatric or internal medicine/pediatric trained physicians should apply. Part-time appointments may be considered. Please send curriculum vitae to: Daniel Torphy, MD, Department of Pediatrics, Medical College of Wisconsin, 170 West Wells Street, Milwaukee, WI 53233. Equal opportunity, affirmative action employer, M/F/H.

DESIRABLE BOSTON SUBURB — BC/BE pediatrician. Share call one weeknight in five, and one weekend in five. Send CV: Donald J. Annino, MD, 955 Main Street, Winchester, MA 01890.

MISSOURI — BC/BE to become fifth pediatrician in a thirty-five physician, multi-specialty clinic. Income guarantee with good long-term potential. Office located in new medical plaza with laboratory and pharmacy. Practice centered in university town with excellent educational, cultural and recreational facilities. Columbia recently ranked among top five cities in nation (by "Money Magazine") for quality of life. Direct inquiries/CV to: Terri Maples, Physician Recruiter, Columbia Regional Hospital, 404 Keene Street, Columbia, MO 65201.

PLEASE NOTE — Address replies to box number ads as follows: Box number, ______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

UTAH — BC/BE pediatrician needed in busy, 18-member multi-specialty group in Logan. Beautiful northern Utah university town. Guaranteed salary with incentive and benefits. Great family oriented and recreational opportunities. Send CV to: Neal Byington, Administrator, Budge Clinic, 225 East 400 North, Logan, UT 84321. (801) 752-0422.

CALIFORNIA—Multi-specialty group practice currently recruiting an additional board-eligible/board-certified pediatrician. Practice is located in a pleasant, northern California community. There are two JCAH approved hospitals. Ample recreational opportunities available, including close proximity to Lake Tahoe and San Francisco Bay area. First year guarantee, plus incentive. Malpractice paid. Send CV with inquiry to: Sharon A. Stone, Administrator, Chico Medical Group, 251 Cohasset Road, Chico, CA 95926.

6.5 PEDIATRICIANS need additional full- or part-time BC/BE pediatrician. Level II nursery. Superb professional and recreational opportunities. Guaranteed salary, eventual partnership. Contact: M. Pankau, MD, (208) 523-3150. 890 Oxford Drive, Idaho Falls, ID 83401.

WASHINGTON— Established, four full-time/two part-time pediatric group seeking full-time BC/BE pediatrician. Beautiful, rapidly growing community in midst of mountains and water, one hour from Seattle. Local hospital and nearby childrens' hospitals. Opportunity to practice a wide range of pediatric skills. Competitive salary; early partnership. Reply with cover letter and CV to: Medical Director, Kitsap Children's Clinic, 2625 Wheaton Way, Suite A, Bremerton, WA 98310. (206) 479-1651.

ENDOCRINOLOGIST/PEDIATRIC—BC/BE. The Cleveland Clinic Foundation, a 500-physician group practice, seeks motivated, energetic pediatrician. Tertiary referral practice, clinical research and residency program. Joint appointment in departments of endocrinology and pediatrics. Send CV/references: Dr. Byron Hoogwerf, Desk A-80, Cleveland Clinic, Cleveland, OH 44195.

Professional Opportunities

PEDIATRICIAN—BE/BC to join three others to cover pediatric unit, newborn ICU and delivery suite in large, progressive, community hospital, with excellent subspecialty support. Competitive salary with liberal fringe benefits including malpractice insurance, paid vacation, education leave and expenses, and health insurance. If interested, please contact: Gordon Borkat, MD, (216) 476-7237. Or send CV to: 18101 Lorain Avenue, Cleveland, OH 44111.

PHOENIX/SCOTTSDALE—Third pediatrician, BC/BE. Competitive salary plus bonus. Fringe benefits, early partnership. Send CV to: Philip A. Bond, MD, 1728 West Glendale Avenue, Phoenix, AZ 85021.

PENNSYLVANIA—Well-established, busy, four-person pediatric practice seeks BC/BE pediatrician. Salary with incentive bonus leading to full partnership. Two community hospitals with Level II nurseries. Contact: Ralph H. Kaiser, MD, 904 Campbell Street, Williamsport, PA 17701. (717) 326-3348.

NEED A DOCTOR? For the most comprehensive coverage to specific specialties and select subspecialties, put your recruitment ad in an AMA specialty journal. We target your ad to the physician you want. To schedule your ad call our "Classified Advertising" office: (800) 237-9851.

CALIFORNIA—NEONATOLOGIST BC/BE. Two positions available with active neonatal group, 12,000 delivery base with tertiary and secondary level positions. Excellent practice opportunity for neonatologist desiring relocation in southern California. Contact: Doctors of Newborn Critical Care, 721 North Euclid Avenue, Suite 308, Anaheim, CA 92801. (714) 772-4822.

PLEASE NOTE—Address replies to box number ads as follows: Box number, _______, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

PEDIATRICIAN

Immediate opportunity to associate with five pediatricians in a 70-doctor multi-specialty group. Drawing area of 400,000. Modern hospital within five minutes of clinic. Stimulating Big-10 university community of 110,000 with superb cultural advantages. Ideal for families. Medical school teaching affiliation if desired. Excellent initial guarantee and fringes with early associate status, subsequent income based exclusively on productivity. Send CV to:

RONALD H. DEERING, MD
Christie Clinic Association
101 West University
Champaign, IL 61820

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Maybe you should consider a pediatric career with The Permanente Medical Group of Northern California.

The Stockton Medical Offices is recruiting pediatricians — five of eleven pediatricians in this department came from fee-for-service.

If interested, please contact:

Jack L. Gilliland, MD
Chief of Pediatrics
The Permanente Medical Group, Inc.
1305 Tommydon Street
Stockton, CA 95210 • (209) 476-3346

Pediatric Subspecialists

The University of South Dakota School of Medicine currently has openings for the following BE/BC pediatric subspecialties:

Cardiology
Pulmonology
Hematology/Oncology
Intensivist
Neurology
Surgery
Neonatology
Infectious Disease

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the healthcare of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

Sioux Falls is located in the geographic center of America with friendly people who exemplify traditional midwestern values. Our community has a strong economic base, growing population and a progressive educational system. Included in David Frankes' book, *America's Fifty Safest Cities*, Sioux Falls also offers numerous cultural opportunities. South Dakota's four season climate welcomes endless recreational activities year-round.

Competitive financial packages offered. EOE/AAE.

Send CV or call:
Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

Professional Opportunities

NORTH CAROLINA—Medical center community. Two certified pediatricians seek third BC/BE for thriving practice. Reply to: Jerry L. Bennett, MD, 2240 Cloverdale Avenue, Suite 217, Winston-Salem, NC 27103.

WASHINGTON — Established two-doctor clinic needs third BC/BE pediatrician. Beautiful coastal community, competitive salary, possible partnership. Send CV, date available: Pediatric Clinic, 611 North F Street, Aberdeen, WA 98520. (206) 533-0408.

Positions Available

THE DEPARTMENT OF PEDIATRICS at the Allegheny Campus of the Medical College of Pennsylvania is seeking BC/BE pediatricians to provide inpatient coverage for hospitalized children. It is an exciting opportunity to provide care for pediatric patients with a wide variety of acute and chronic illnesses. Other duties include teaching medical students and residents. Research opportunities are available. If interested send curriculum vitae or contact: Adrian Dana, MD, Director Inpatient Pediatrics, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212. Telephone: (412) 359-3161.

Directors Wanted

DIRECTOR OF PEDIATRIC EDUCATION sought for faculty of top-notch, accredited family practice residency program. Responsibilities include teaching rounds, overseeing patient care and pediatric clinic, research and medical student teaching. Successful candidate will be residency-trained and recent graduates are encouraged to apply. Opportunity is located in northwestern Pennsylvania, an area which offers lakeside living, good schools, an abundance of recreational activities, and an excellent quality of life. Contact: Danette Mazur, Hamot Medical Center, 201 State Street, Erie, PA 16550. (814) 870-7045.

Directors Wanted

NEONATAL CO-DIRECTOR sought: BC/BE neonatologist for fee-for-service private practice in Level II, 18-bed nursery with 1,800 plus deliveries. Clinical, administrative and minimal teaching responsibilities (medical school and family practice residency). 150-bed, referral hospital located in southern Illinois university city. Great educational and recreational opportunities. Call Georgetta: (800) 328-3666.

Faculty Positions

NEW MEXICO

Pediatric Infectious Disease faculty position at the University of New Mexico School of Medicine; tenure-line, appointment level commensurate with experience. Duties will include teaching (medical students/residents), patient care and research. Ample opportunities for collaborative research endeavors are available. Highly representative patient population. Interested applicants should contact:

John Johnson, MD, Chairman
Department of Pediatrics
University of New Mexico School of Medicine
Albuquerque, NM 87131
Telephone: (505) 277-5551

The University of New Mexico is an equal opportunity employer.

PEDIATRIC HEMATOLOGIST/ONCOLOGIST — Loyola University of Chicago, Stritch School of Medicine, Department of Pediatrics, is recruiting an Assistant Professor for the Section of Hematology/Oncology. Applicant must be sub-board certified or eligible, with expertise in hematology/oncology research. Interested applicants are invited to send their CV to: Carlos R. Suarez, MD, Director, Section of Pediatric Hematology/Oncology, 2160 South First Avenue, Maywood, IL 60153. Loyola University of Chicago is an equal opportunity educator and employer. Qualified persons are not subject to discrimination on the basis of a handicap.

Medical Director

Children's Rehabilitation Unit

The Department of Pediatrics, University of Kansas Medical Center is seeking a full-time pediatrician in developmental pediatrics and/or child neurology, with demonstrated research productivity as well as administrative ability. The candidate will be responsible for all of the administrative organization and tasks as well as be involved in medical evaluation and consultation for patients seen in the Children's Rehabilitation Unit. The Children's Rehabilitation Unit is a part of the Kansas University affiliated programs. Rank and salary will be commensurate with experience and training. Interested applicants should send their curriculum vitae to:

Allen Erenberg, MD, Chairman
Department of Pediatrics
University of Kansas Medical Center
3900 Rainbow Boulevard
Kansas City, KS 66103
(913) 588-6339
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Seeking board-certified or board-eligible pediatricians to provide part-time or full-time ambulatory services.

Responsibilities may include emergency room, child sexual abuse, transport, house coverage, or other services based on interest.

Our 153-bed hospital, Louisiana's only full service pediatric facility, provides multi-disciplinary care to patients from Louisiana and the Gulf South.

New Orleans offers a warm climate, a variety of entertainment and leisure activities, and the country's best food and music.

Louisiana license or qualification for licensure required. For consideration, send CV to:

Alan Robson, MD
Medical Director
Children's Hospital
200 Henry Clay Avenue
New Orleans, LA 70118

Faculty Positions

AMBULATORY PEDIATRIC MEDICINE—The Division of Ambulatory Medicine, Children's Hospital of The King's Daughters, is seeking additional faculty beginning July 1991. Responsibilities include: resident and medical student teaching, direct patient care and clinical research. Outpatient visits for 1989-1990 totaled approximately 50,000. Academic appointment with Eastern Virginia Medical School commensurate with experience. Please contact: John M. de Triquet, MD, Children's Hospital of The King's Daughters, Ambulatory Pediatric Medicine, 800 West Olney Road, Norfolk, VA 23507. (804) 628-7179.

ACADEMIC PEDIATRIC CARDIOLOGIST—The Department of Pediatrics, East Carolina University School of Medicine, is seeking a BC/BE pediatric cardiologist to join a rapidly growing and busy three-member section of pediatric cardiology. Responsibilities include patient care, teaching, and clinical or laboratory research. Applicants of all faculty rank will be considered. Outdoor recreation activities abound in this pleasant, near-coastal community. Send letter of inquiry and CV to: Jon B. Tingelstad, MD, Professor and Chairman, Department of Pediatrics, East Carolina University School of Medicine, Greenville, NC 27858-4354. Federal law requires proper documentation of identity and employability at the time of employment. It is requested that this documentation be included with your application. AA/EEO.

Practices Available

TEXAS—Eighteen-year-old, busy, solo pediatrics practice available. Three minutes outside Dallas, family oriented community, easily accessible to medical centers. Call: Dr. Gray, (214) 296-9930.

Computers/Software

PRACTICE MANAGEMENT, insurance billing, medical records, and electronic claims systems. American Medical Software (800) 423-8836.

NEONATOLOGISTS

The Department of Pediatrics, University of Texas Medical School at Houston is seeking additional full-time faculty for the Division of Neonatal-Perinatal Medicine.

The division has an active fellowship training program, faculty with diverse research interests and excellent clinical facilities. Three distinct types of faculty appointments are available:

1) A traditional academic track with a commitment to basic investigative opportunities
2) An academic track centering on clinical investigative activities at one of our two, state-of-the-art, tertiary care care hospitals (Hermann Children's Hospital and Lyndon Baines Johnson General Hospital), and
3) A clinical track at one of three intermediate care units in community hospitals.

Applicants should be BC/BE in neonatal-perinatal medicine. Faculty rank commensurate with previous experience.

The University of Texas is an equal opportunity employer. Women and minorities are encouraged to apply.

Contact:

Susan E. Denson, MD
Department of Pediatrics
University of Texas Medical School
P.O. Box 20708
Houston, TX 77225 • (713) 792-5342

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COVERAGE[1,2] AND CONVENIENCE[3-6] NO OTHER ORAL ANTIBIOTIC CAN OFFER

- ***Broad in vitro† spectrum[1,2]***
- ***Highly active against key respiratory pathogens†[7-9]***
- ***Proven effective in clinical trials[1,10-13]***

* Due to susceptible organisms.

† Although a useful guide, *in vitro* activity may not correlate with clinical response.

SUPRAX may be administered as a single dose, once a day, or in divided doses bid if preferred.

References: 1. Data on file, Lederle Laboratories, Pearl River, NY. **2.** Neu HC: Beta-lactamase stability of cefixime. *Internal Medicine* 1990;11:57-71. **3.** A national study of consumer experience with antibiotic herapy. Princeton, NJ, The Gallup Organization, Inc., July 1989. Data on file, Lederle Laboratories, Pearl River, NY. **4.** Cockburn J, Gibberd RW, Reid AL, et al: Determinants of non-compliance with short term antibiotic regimens. *Br Med J* 1987;295:814-818. **5.** Hussar DA: Importance of patient compliance in effective antimicrobial therapy. *Pediatr Infect Dis J* 1987;6:971-975. **6.** Greenberg RN: Overview of patient compliance with medication dosing: A literature review. *Clin Ther* 1984;6:592-599. **7.** Neu HC, Chin N-X, Labthavikul P: Comparative *in vitro* activity and ß-lactamase stability of FR 17027, a new orally active cephalosporin. *Antimicrob Agents Chemother* 1984;26:174-180. **8.** Neu HC: *In vitro* activity of a new broad spectrum, beta-lactamase-stable oral cephalosporin, cefixime. *Pediatr Infect Dis J* 1987;6:958-962. **9.** Sanders CC: ß-lactamase stability and in vitro activity of oral cephalosporins against strains possessing well-characterized mechanisms of resistance. *Antimicrob Agents Chemother* 1989;33:1313-1317. **10.** Pichichero ME: Cefixime multicenter national otitis media study, In *The Contemporary Treatment of Otitis Media* 1990. Lederle Laboratories. Data on file, Lederle Laboratories, Pearl River, NY. **11.** Howie VM, Owen MJ: Bacteriologic and clinical efficacy of cefixime compared with amoxicillin in acute otitis media. *Pediatr Infect Dis J* 1987;6:989-991. **12.** Verghese A, Roberson D, Kalbfleisch JH, et al: Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. *Antimicrob Agents Chemother* 1990;34:1041-1044. **13.** Kiani R, Johnson D, Nelson B: Comparative, multicenter studies of cefixime and amoxicillin in the treatment of respiratory tract infections. *Am J Med* 1988;85:6-13.

Please see brief summary of Prescribing Information on adjacent page.

SUPRAX® cefixime/Lederle

BRIEF SUMMARY. Please see package insert for full Prescribing Information

INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes.**

Note: For information on otitis media caused by *Streptococcus pneumoniae,* see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S pneumoniae* and *H influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S pyogenes.*

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis.*

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *B catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *B catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime[(a)] 4 mg/kg bid	Cefixime[(a)] 8 mg/kg qd	Control[(a)] drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1[(b)]
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
Streptococcus pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION.**)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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